October 2017

A 38-year-old Guinean-American female presented to the emergency department (ED) of her local hospital 3 days after returning to the United States from a 1-month trip to Niantanina, Guinea. At the time of presentation, she complained of sudden-onset exhaustion, fever, chills, sore throat, chest pain, severe headache, and infrequent episodes of vomiting and non-bloody diarrhea that began 1 day after returning to the U.S. She explained that while in Guinea she stayed with relatives in a dirt-floor hut and had eaten a diet consisting of local delicacies, including monkey meat, and locally farmed fruits and vegetables. She denied contact with wild animals, but mentioned that she had sustained numerous mosquito bites on a daily basis, had removed at least 5 embedded ticks from her body, and remembered seeing a number of rats, mice, and other small mammals in and around huts within her family's village. She also divulged that she was not consistently compliant with taking her malaria prophylaxis, believing that she would be okay without doing so. However, once she became ill, she suspected that she did in fact contract malaria, prompting her eventual visit to the ED. She denied having sexual intercourse while in Guinea and did not report having contact with other sick individuals. The patient's past medical history was unremarkable.

A physical examination revealed abdominal tenderness secondary to mild hepatomegaly, conjunctivitis, and a fever of 39.8°C. Fearing that the patient had malaria, she was admitted for continuous observation and was started on a course of atovaquone-proguanil. In addition, a course of empiric antibiotic therapy was administered due to a concern for enteric fever. Laboratory testing revealed lymphopenia, thrombocytopenia, elevated aspartate and alanine aminotransferases, and proteinuria. However, tests for malaria, bacteremia, and for agents of gastrointestinal and respiratory tract infections were negative. Over the next 7 days, the patient's health deteriorated. She developed facial edema, bloody diarrhea, bleeding from the gums and from venipuncture sites, and she eventually became extremely lethargic. At this time, the patient was transferred to an isolation room where she was treated by personnel adhering to strict barrier precautions. Blood specimens for yellow fever, dengue, leptospirosis, Ebola virus disease, Marburg hemorrhagic fever, Crimean-Congo hemorrhagic fever, and Lassa fever serological testing and PCR were submitted to the Centers for Disease Control and Prevention (CDC). While awaiting test results, the patient was started on ribavirin, but she became unresponsive and eventually died on the morning of the 8th day of hospitalization. The following morning, the CDC confirmed the diagnosis of Lassa fever by real-time RT-PCR that was performed using a remnant blood specimen collected during the patient's presentation to the ED and by IgM ELISA that was performed on a blood specimen collected 2 days prior to the patient's death.

Based upon your knowledge of the ecology and transmission of Lassa virus, which of the following scenarios most likely accounts for how this patient became infected?

A. The patient most likely contracted Lassa virus from a casual encounter with an asymptomatic human carrier of the virus.
B. The patient most likely was infected through consumption of undercooked bush meat.
C. The patient most likely contracted Lassa virus from a mosquito or tick bite.
D. The patient was most likely exposed to the virus through contact with contaminated rodent excreta.
E. None of the aforementioned scenarios would predispose her to infection, as Lassa virus is transmitted by the bites of infected insectivorous bats.

Intended Response

D. The patient was most likely exposed to the virus through contact with contaminated rodent excreta.

Explanation and Discussion

Although person-to-person transmission of Lassa virus (LASV) is well-documented, the majority of LASV infections occur as a consequence of exposure to contaminated rodent excreta. Option A is incorrect because an asymptomatic carrier state is not known to exist in humans. In addition, LASV is not known to be transmitted through ingestion of undercooked non-human primate meat or through the bites of hematophagous arthropods or insectivorous bats, eliminating options B, C, and E.

Lassa fever was first described in 1969 among missionary nurses in Nigeria, one of whom contracted the disease from a patient in the town of Lassa, the eponym of LASV, in northeastern Nigeria (1). Since that time, LASV has been associated with approximately 100,000 – 300,000 cases per year, of which nearly 5,000 are fatal (2). Although Lassa fever does not occur naturally outside of West Africa, cases have been exported to Europe and the United States within the past 17 years. The majority of human cases (~80%) manifest with clinically unapparent or mild symptoms, but a range of moderate to severe symptoms, including facial edema and hemorrhaging from mucous membranes, the eyes, and other sites, can develop in the remaining 20% of patients. Death is most commonly caused by multiorgan failure within 2 weeks of symptom onset (2). In nature, LASV is carried by rodents known as multimammate rats (*Mastomys natalensis*), and the virus is shed in their urine and droppings. Inhalation of LASV-laden excrement aerosols and consumption of excrement-contaminated foods are well-known means of LASV transmission, and these appear to be the most common forms of transmission as *M. natalensis* readily colonizes human habitats in disease-endemic regions.

LASV is a member of the Old World, or LCMV/LASV, complex of viruses belonging to the genus *Mammarenavirus*, family *Arenaviridae*. Other viruses within this complex include lymphocytic choriomeningitis virus and Lujo virus, both human pathogens, among others. These viruses possess minus-sense, single-stranded RNA genomes divided into two segments, designated L (for Large) and S (for Small), that measure approximately 7.5 kbp and 3.5 kbp, respectively. Virions are comprised of both L and S genomic segments encapsidated by numerous copies of the viral nucleoprotein (N). Nucleocapsids are associated with copies of the RNA-dependent RNA-polymerase (L), which are bound to a promoter on both genomic segments. The complete ribonucleocapsids are enveloped by matrix protein (Z)-lined and glycoprotein (GP)-studded lipid bilayer membrane that is acquired by budding from the plasma membrane. The transmembrane GP spikes are responsible for adsorption of particles to host cells via interaction with the host cytoplasmic membrane protein α-dystroglycan (3).

LASV infection can be diagnosed by a number of means, including detection of viral RNA by RT-PCR, by viral culture, by serological testing for virus-specific IgM and IgG, and by immunohistochemical staining if post-mortem tissue specimens are available for analysis (2, 4). Optimal detection of LASV RNA via PCR requires testing blood specimens early in the disease process, and viral culture should not be attempted outside of the confines of a maximum containment laboratory, as LASV is a risk group-4 pathogen and a select agent. In the U.S., testing for LASV is available at the CDC, so American healthcare providers interested in testing patients should seek diagnostic assistance from their local and state health department laboratories who can, in turn, forward specimens to the CDC. Treatment of Lassa fever early in the disease process with ribavirin has proven successful and prevention of LASV transmission is contingent upon

elimination of multimammate rat colonization of human domiciles and adherence to strict barrier care practices (e.g., wearing protective clothing, including gloves, face and body protection, etc.) when caring for the sick.

Suggested Reading / References:

1. **Frame JD, Baldwin Jr JM, Gocke DJ, Troup JM.** 1970. Lassa fever, a new virus disease of man from West Africa I. clinical descriptions and pathological findings. Am J Trop Med Hyg. 19:670-676.

2. **Centers for Disease Control and Prevention.** Lassa fever: https://www.cdc.gov/vhf/lassa/index.html. Last accessed, July 16, 2017.

3. **Buchmeier MJ, de la Torre J-C, Peters JC.** 2013. *Arenaviridae*, p 1283-1303. *In* Cohen JI, Griffin DE, Lamb RA, Martin MA, Racaniello VR, Roizman B (ed), Fields Virology, 6th ed, vol 2. Lippincott, Williams, & Wilkins, Philadelphia, PA.

4. **Raabe V, Koehler J.** 2017. Laboratory diagnosis of Lassa fever. J Clin Microbiol. 55:1629-1637.

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