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Atypical Chikungunya Virus Infections in Immunocompromised Patients

To the Editor: Chikungunya fever was first described in Tanganyika (now Tanzania) in 1952 and is now emerging in Southeast Asia. Chikungunya virus (CHIKV) infection, a self-limiting febrile illness, shares similarities with dengue fever such as headache and myalgia. Additionally, patients with CHIKV infection typically have arthralgia, arthritis, and tenosynovitis (*1*). Although usually benign, CHIKV infection may on rare occasions lead to neurologic and hepatic manifestations with high illness and mortality rates (*2*). We report 2 immunocompromised patients with CHIKV infection associated with peritonitis, encephalitis, and secondary bacterial infections.

Patient A, a 66-year-old Singaporean-Chinese man, had a history of chronic renal disease secondary to obstructive uropathy. His baseline creatinine level was 300–400 μmol/L. For 3 years, he had ingested traditional Chinese medicine, which we suspect was contaminated by steroids because he appeared cushingoid. An outbreak of CHIKV infection was reported at his workplace. He was admitted to National University Hospital, Singapore, in July 2008 with abdominal pain, vomiting, and fever of 1 day. He had no joint symptoms. Clinically, he had systemic inflammatory response syndrome complicated by acute-on-chronic renal failure. His creatinine level was elevated at 921 μmol/L on admission. A complete blood count showed leukocytosis (19.24×10^9 cells/L) with neutrophilia and thrombocytopenia (62×10^9 cells/L). Initial blood and urine cultures and serologic results were negative for dengue virus, but serum reverse transcription–PCR (RT-PCR) and indirect immunofluorescent assay for immunoglobulin G (IgG) (Euroimmun Medizinische Labordiagnostika, Lubeck, Germany) and IgM (CTK Biotech, Inc, San Diego, CA, USA) were positive for CHIKV (*3*,*4*). Computed tomographic scans of the abdomen showed dilated small bowel loops.

An urgent laparotomy did not show bowel perforation, but peritoneal cultures yielded *Klebsiella pneumoniae*, *Escherichia coli,* and *Candida glabrata*, and RT-PCR from the concentrated peritoneal fluid was positive for CHIKV (*3*). He was administered appropriate antimicrobial drugs. He required repeat laparotomies because of elevated intraabdominal pressure. He subsequently received broad spectrum antimicrobial drugs to treat secondary intraabdominal infections caused by *P. aeruginosa* and *Enterococcus faecalis*.

Ventilator-associated pneumonia also developed. Despite maximal support and prolonged antimicrobial therapy, this patient died after 5 months of hospitalization.

Patient B, a 45-year-old Malaysian–Chinese man with diabetes mellitus, had undergone a cadaveric liver transplant in 2001 for hepatitis B liver cirrhosis. He was receiving immunosuppressants (azathioprine and prednisolone). He was admitted in August 2008 after experiencing fever, headache, and abdominal bloating for 3 days. He had no neurologic symptoms. Acute self-limiting febrile illnesses with arthritis had occurred in his hometown; CHIKV infections were suspected.

Results of his examination on admission were normal, except for bilateral enlarged cervical lymph nodes. Chest radiograph results were unremarkable. He had mild transaminitis (alanine aminotransferase 173 U/L, aspartate aminotransferase 170 U/L), elevated C-reactive protein (107 mg/L), and thrombocytopenia (120×10^9 cells/L) without leukocytosis. Results of comprehensive serum and urine microbial studies were negative for posttransplant infections. Results of serum RT-PCR were negative for CHIKV, but IgG and IgM tests were positive for CHIKV.

Brain magnetic resonance imaging was performed because of the patient's persistent severe headache and transient drowsiness. It showed several nonspecific areas of enhancement, which suggested encephalitis, given the clinical scenario (Figure). However, a lumbar puncture was not performed, and hence, whether the patient's cerebrospinal fluid contained CHIKV could not be determined. Bilateral frontoparietal white matter lesions with restricted diffusion has been suggested as an early sign of viral encephalitis (*5*). However, a retrospective series demonstrated that, in CHIKV encephalitis, abnormalities on magnetic resonance imaging were uncommon, and no pathognomonic features were found (*6*).

Hospital-acquired pneumonia also developed and was treated with broad-spectrum antimicrobial drugs. Bron-

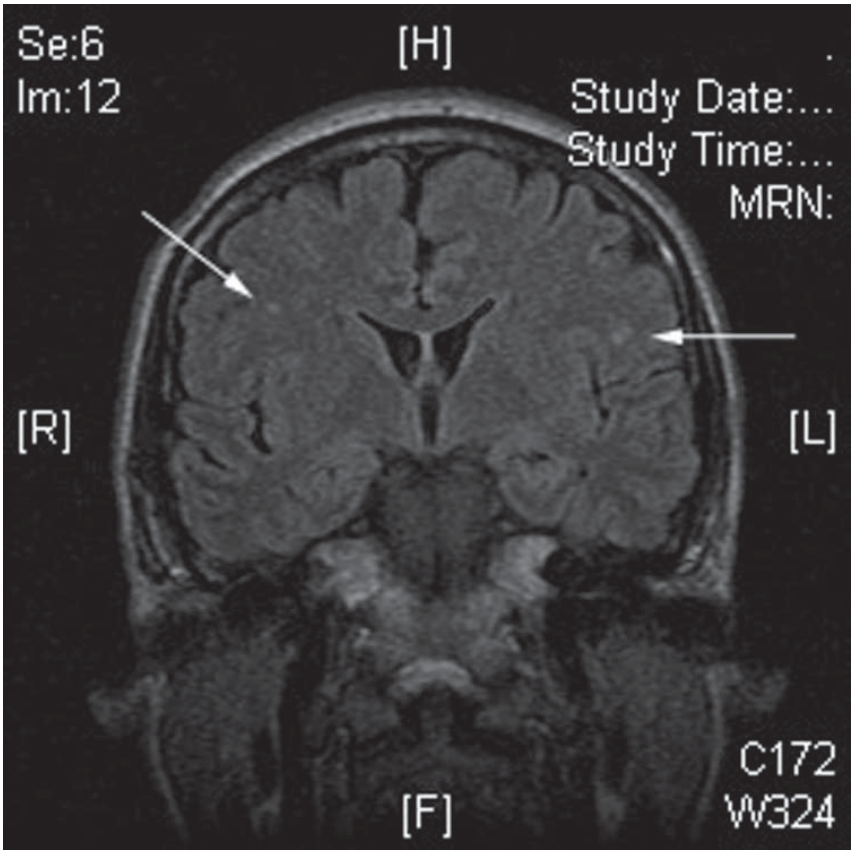

Figure. Magnetic resonance imaging of the brain of patient B, showing several nonspecific areas of enhancement (arrows), which suggests encephalitis, given the clinical scenario.

choscopic cultures were negative for CHIKV. The patient responded well to antimicrobial drugs, and his mental status was normal on discharge. He possibly had encephalitis associated with CHIKV infection, complicated by secondary hospital acquired pneumonia.

In this case, CHIKV was detected in peritoneal fluid, but because of the positive bacterial cultures, we are not confident about its causative role in Patient A's peritonitis. Although a series reported that 6 patients with CHIKV infection had perforated jejunal diverticula while receiving long-term nonsteroidal antiinflammatory drugs and steroids (*7*), the perforations were likely secondary to prolonged steroid use rather than CHIKV infection. In addition, both immunocompromised patients in our study had their CHIKV infections secondarily complicated by nosocomial infections. We note that other viral infections have been associated with bacterial translocation and secondary nosocomial infections (*8*). Whether these infections were linked to CHIKV infection or to the underlying chronic immunosuppressed state is unclear.

Both of our patients did not have the joint manifestations that are characteristic of CHIKV infection (*9*). More prospective studies are required to determine the full spectrum of clinical features of CHIKV infection in immunocompromised patients. Recently identified biomarkers may predict patients at risk for complications but we were unable to study them in our patients (*10*). Although most cases of CHIKV infection are self-limiting, clinicians should be alert to atypical presentations and severe complications in immunosuppressed patients.

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Lassa Fever, Nigeria, 2005–2008

To the Editor: Lassa fever affects ≈100,000 persons per year in West Africa (*1*). The disease is caused by Lassa virus, an arenavirus, and is associated with bleeding and organ failure. The case-fatality rate in hospitalized patients is 10%–20%. The reservoir of the virus is multimammate mice (*Mastomys natalensis*). Investigations in the 1970s and 1980s pointed to the existence of 3 disease-endemic zones within Nigeria: the northeastern region around Lassa, the central region around Jos, and the southern region around Onitsha (*2*,*3*). The current epidemiologic situation is less clear because no surveillance system is in place.

In 2003 and 2004, we conducted a hospital-based survey in Irrua, which demonstrated ongoing transmission of the virus in Edo State, Nigeria (*4*). Since then, laboratory capacity at the University of Lagos for diagnosing Lassa fever has been improved and used for small-scale passive surveillance in other parts of the country. Public health officials or hospital staff reported suspected cases. Blood samples were sent to Lagos, or staff from Lagos collected samples on site. Confirmatory testing, sequencing, and virus isolation were performed at the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany. Primary testing was done by reverse transcription–PCR (RT-PCR) that targeted the glycoprotein (GP) gene (*5*,*6*). An RT-PCR that targeted the large (L) gene was used as a secondary test (*7*), and PCR products were sequenced. Serologic testing for Lassa virus–specific immunoglobulin (Ig) G and IgM was performed by immunofluorescent antibody test using Vero cells infected with Lassa virus. Virus isolation with Vero cells was conducted in the BioSafety Level 4 laboratory in Hamburg.

From 2005 through 2008, 10 cases of Lassa fever were confirmed by virus detection (cases 3–10) or implicated by epidemiologic investigation and serologic testing (cases 1 and 2) (online Appendix Table, www.cdc.gov/EID/content/16/6/1040-appT.htm). Case-patients 1–4 were involved in a nosocomial outbreak that occurred in February 2005 at the Ebonyi State University Teaching Hospital (EBSUTH) in Abakaliki. Retrospective investigation suggests the following transmission chain. The presumed index case-patient was a male nurse living in Onitsha, who became ill on January 21, 2005, and traveled ≈200 km to EBSUTH for better medical treatment. The detection of Lassa virus–specific IgM during his convalescent phase indicates that he had Lassa fever. The second case-patient was a female nurse who had contact with the index case-patient on February 4. She was admitted on February 7 and died 6 days later. Her clinical features were compatible with Lassa fever, but laboratory confirmation is lacking because specimens were not collected. Two additional case-patients among hospital staff (case-patients 3 and 4) were seen on February 21; each had had contact with case-patient 2. Case-patient 3 took care of case-patient 2 and slept in the same room with her for 4 days. Lassa fever was confirmed in case-patients 3 and 4 by RT-PCR as well as by IgM and IgG seroconversion in the surviving patient (case-patient 3). Case-patient 4, a pregnant nurse, had a spontaneous abortion and died on day 9 of hospitalization. Sequencing the GP and L gene PCR fragments showed that case-patients 3 and 4 were infected with the same virus strain (100% identity). In March and April 2005, blood was collected from 50 hospital staff members (including those who had had contact with the case-patients) and screened for Lassa virus–specific IgM and IgG. No positive blood samples were found, which indicated that no additional staff members were involved in the outbreak.

Case-patients 5 and 6 were admitted to EBSUTH in 2008 on January 17 and March 5, respectively. Both were medical doctors, one at a local hospital and the other at EBSUTH, and both died. Encephalopathy with generalized seizures and loss of consciousness preceded death in both cases. The source of infection is unknown, although it is likely that they became infected while they treated patients without knowing they had Lassa fever. In agreement with the epidemiology, the viruses from the 2 patients were similar, though not identical (89% and 87% identity in the GP and L genes, respectively).

Cases 7 to 10 occurred in Abuja and Jos from December 2007 through March 2008. Healthcare workers appeared not to be involved, and no molecular epidemiologic evidence indicated that transmission occurred among the 3 case-patients from Jos (94–97% and 90–94% identity in the GP and L genes, respectively).

In conjunction with our previous report (*4*), the cases presented here demonstrate current Lassa fever activity in the states of Edo, Ebonyi, Federal Capital Territory, and Plateau. These findings correspond to early re-