

# Encephalitis Caused by Chikungunya Virus in a Traveler from the Kingdom of Tonga

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**Febrile travelers from countries with unique endemic pathogens pose a significant diagnostic challenge. In this report, we describe the case of a Tongan man presenting with fever, rash, and altered mental status. The diagnosis of Chikungunya encephalitis was made using a laboratory-developed real-time RT-PCR and serologic testing.**

## CASE REPORT

In March 2014, a 57-year-old man from the Island of Tongatapu, Tonga, with no significant past medical history presented to our institution with 1 day of fever and altered mental status. He had been in his usual state of health until 1 week prior, when he developed diffuse joint pains, headache, and mild abdominal pain. He subsequently traveled from Tonga to California, USA, to visit family. One day prior to admission, he complained of chills, and on the day of admission, he was noted to have altered mental status and was brought to the hospital. His exposure history was notable for recent mosquito bites and a sick contact with similar joint pains and fever. He had no other significant exposures. In the week prior to admission, the Tongan Ministry of Health reported a spike in cases of patients presenting with a systemic febrile illness and a rash. A virus was the presumed cause of the outbreak, with initial consideration given to dengue, Zika, or measles viruses.

On initial exam, the patient had an erythematous papular rash on his abdomen with numerous, scattered petechiae over his trunk; the rash spared his palms and soles. He was nonverbal and did not follow commands. The patient had a witnessed tonic-clonic seizure and developed a temperature of 38.7°C. His white blood cell (WBC) count was 5,900/ $\mu$ l with 5 to 10% reactive lymphocytes and an otherwise normal differential. Other laboratory studies included the following: hemoglobin level of 13.9 g/dl, platelet count of 196,000/ $\mu$ l, creatinine level of 1.3 mg/dl, and liver function tests within normal limits. Urinalysis showed no evidence of infection; urine toxicology screen was negative. A lumbar puncture was performed during his evaluation in the emergency department. This revealed an opening pressure of 27 cmH<sub>2</sub>O, 4 WBC/ $\mu$ l, 3 red blood cells/ $\mu$ l, glucose of 124 mg/dl (serum, 184 mg/dl), and protein level of 196 mg/dl. The patient was admitted to the intensive care unit and intubated for airway protection. Magnetic resonance imaging of the brain was notable for incomplete suppression of cerebral spinal fluid (CSF) spaces along bilateral occipital lobes. Electroencephalography (EEG) showed moderate diffuse slowing.

Bacterial cultures from blood, urine, and CSF were negative. The following infectious disease testing was performed and was negative: fourth-generation HIV antibody/antigen screen; serum IgM for dengue (DENV), West Nile (WNV), measles, and rubella viruses; syphilis enzyme immunoassay; CSF WNV IgM; and CSF PCRs for enterovirus, herpes simplex virus, Epstein-Barr virus,

varicella-zoster virus, and cytomegalovirus. The patient de-escalated on the second hospital day; he improved with supportive care, initiation of antiepileptic drugs, and three doses of intravenous immunoglobulin.

Given this patient's travel history and potential exposures, laboratory-developed nucleic acid amplification tests were performed for DENV, *Plasmodium falciparum*, *Plasmodium* species, Zika virus, and *Leptospira* species (1). No amplification was observed.

Specimens were then tested for Chikungunya virus (CHIKV) RNA, targeting the nonstructural protein 2 gene. This testing was performed as part of a laboratory-developed, multiplex, real-time, reverse transcriptase PCR (rRT-PCR) that also targets DENV, yellow fever virus (YFV), and Rift Valley fever virus (RVFV). Samples tested for CHIKV included four EDTA plasma samples obtained on hospital days 1, 3, 4, and 5, one serum sample (gold top) obtained on day 2, and CSF. CHIKV RNA was detected, with late cycle threshold ( $C_T$ ) values (range of 35.53 to 37.50), in all plasma and serum samples tested. The patient's CSF tested negative. DENV, YFV, and RVFV were not detected in any sample. On hospital day five, serum anti-CHIKV IgM and IgG were positive at titers of 1:80 and 1:5,120, respectively (reference, <1:10; Focus Diagnostics, Cypress, CA).

Following the patient's hospitalization, the results of CHIKV antibody testing, performed at the Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases (Fort Collins, CO), became available. Anti-CHIKV IgM was detected by IgM capture enzyme-linked immunosorbent assay (ELISA) in serum from hospital day two. Results of serum anti-CHIKV IgG ELISA were uninterpretable due to high background, though the plaque reduction neutralization test (PRNT) was negative. CHIKV RNA was not detected in CSF using the CDC rRT-PCR. However, anti-CHIKV IgM was detected in CSF by IgM

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capture ELISA, whereas anti-DENV and anti-Zika virus IgM antibodies were not detected.

CHIKV is an alphavirus transmitted by *Aedes* species mosquitoes (2). Symptomatic CHIKV infections typically result in a self-limited systemic febrile illness associated with rash and arthralgia (2–4). However, cases of severe disease, including meningoencephalitis and death, have also been reported (3–5). Importantly, CHIKV may present similarly to numerous other infectious causes of systemic febrile illness in the tropics, including malaria, dengue, and other arthropod-borne infections. This case in particular was complicated by ongoing regional transmission of DENV and Zika virus in Oceania, as well as the emergence of measles in Tonga and California, USA. The diagnosis of Chikungunya infection in this Tongan man was ultimately made using a laboratory-developed CHIKV rRT-PCR and reference serologic testing, though additional culture-based, molecular, and serologic tests were critical to rule out other potential infectious causes of encephalitis.

While encephalitis represents an atypical presentation of Chikungunya fever, the clinical, radiologic, and laboratory findings support the diagnosis in this case (6). CHIKV RNA was detected from plasma and serum samples collected over the first 5 days of our patient's hospitalization, and the low-level viremia is consistent with his late presentation (7). During the Réunion Island CHIKV outbreak in 2005 and 2006, atypical cases of Chikungunya fever, including encephalitis, increased with patient age. Consistent with the age of our patient, 57 years old, the highest incidence of atypical cases in the Réunion Island series was among patients 45 to 64 and  $\geq 65$  years old (8). Furthermore, similar to our patient, eight of 12 patients in the series who developed seizures had no underlying neurological disease (8). Evaluation of CSF from patients with Chikungunya encephalitis has revealed elevations in protein and WBC (often  $<100/\mu\text{l}$ ), with a predominance of mononuclear cells (5, 9). Though the WBC count was normal in our case, CSF protein levels were elevated. Finally, CHIKV RNA was not detected in CSF from this case, which is consistent with previous reports that documented inconsistent CHIKV RNA detection in the CSF of patients with meningoencephalitis (5, 9).

After the diagnosis was made and the patient was discharged, samples from patients in Tonga, presenting during the current outbreak with a systemic febrile illness and a rash, also tested positive for CHIKV (10). Following the outbreak on Réunion Island, CHIKV has spread throughout many of the countries of the Indian Ocean and South Pacific (2, 3, 11). However, to our knowledge, CHIKV has not been previously detected in Tonga, and the most recent serological survey, performed in 1975, identified little exposure to CHIKV in the South Pacific at that time (12). The potential for CHIKV outbreaks in Oceania has been well documented, however, and the vectors, *Aedes albopictus* and *Aedes aegypti*, are present in Tonga (11, 13, 14). The current outbreak likely resulted from the introduction of CHIKV into a naive population, either from a viremic traveler or the incidental transportation of infected mosquito vectors.

In summary, this is a case of Chikungunya encephalitis in a traveler from the Kingdom of Tonga, whose diagnosis was complicated by ongoing regional transmission of several viral pathogens responsible for undifferentiated systemic febrile illnesses.

The diagnosis of Chikungunya encephalitis preceded the identification of CHIKV by the Tongan Ministry of Health as the etiologic agent of the current outbreak on the Island of Tongatapu. As such, this case confirms the sentinel role that clinical microbiology and virology laboratories can play in the global surveillance for emerging infectious diseases. This case further highlights the utility of sensitive multiplex diagnostics for the detection of pathogens that cause an undifferentiated systemic febrile illness, which is a common clinical syndrome among patients residing in or recently returned from tropical and subtropical regions of the world (1, 15). With the spread of CHIKV throughout the South Pacific, the recent introduction of CHIKV to the Caribbean Islands (16), and the high prevalence of infection in Africa, South Asia, and Southeast Asia, CHIKV should be considered in the differential diagnosis of travelers presenting with fever as well as febrile patients in regions where it is endemic.

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