Am. J. Trop. Med. Hyg., 95(4), 2016, pp. 894–896
doi:10.4269/ajtmh.16-0323

Case Report: Zika Virus and Chikungunya Virus CoInfections: A Series of Three Cases from a Single Center in Ecuador

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Abstract. Zika virus (ZIKV) and chikungunya virus (CHIKV) cocirculate throughout much of the tropical Western Hemisphere; however, few cases of coinfection with these two pathogens have been reported. Herein, we describe three cases of ZIKV–CHIKV coinfection detected at a single center in Ecuador: a patient who developed symptoms on postoperative day 5 from an orthopedic procedure, a woman who had traveled to Ecuador for fertility treatment, and a woman who was admitted for Guillain–Barré syndrome and had ZIKV and CHIKV detected in serum and cerebrospinal fluid. All cases were diagnosed using a multiplex real-time reverse transcription polymerase chain reaction, and ZIKV viremia was detected as late as 16 days after symptom onset. These cases demonstrate the varied clinical presentation of ZIKV–CHIKV coinfections as well as the importance of multiplexed arboviral testing for these pathogens.

INTRODUCTION

Before a well-described outbreak on Yap Island, Micronesia, in 2007, Zika virus (ZIKV) was a relatively obscure flavivirus that was only recognized as the cause of sporadic human infections in Africa and southeast Asia.[1,2] Since then, ZIKV has spread across islands in the Pacific Ocean and into the Western Hemisphere, in a pattern similar to the spread of chikungunya virus (CHIKV) a few years earlier.[2] As a result, ZIKV now cocirculates with CHIKV and dengue virus (DENV) in many regions of the Americas.

Symptomatic ZIKV infections often present with some combination of fever, joint pain, myalgia, headache, conjunctivitis, and a pruritic rash.[1,3] During the ongoing outbreak, ZIKV has also been associated with severe manifestations, namely fetal microcephaly and Guillain–Barré syndrome (GBS).[4–6] The potential for such severe outcomes demonstrates the need for accurate ZIKV diagnostics. However, ZIKV diagnosis remains a challenge due to the considerable overlap in clinical presentations caused by ZIKV, CHIKV, and DENV as well as false-positive results using available anti-DENV IgM and DENV nonstructural protein-1 assays.[2] In addition, the majority of ZIKV infections, up to 80% in some series, remain asymptomatic.[1,2]

Limited data exist regarding ZIKV coinfections, which cannot be ruled out without specific testing for each virus, and only three cases have been well characterized in the literature.[7,8] In this report, we describe three ZIKV–CHIKV coinfections that were diagnosed in early 2016 at the Hospital Luis Vernaza in Guayaquil, Ecuador. Cases were detected using a single-reaction, internally controlled, multiplex real-time reverse transcription polymerase chain reaction (RT-PCR) for ZIKV, CHIKV, and DENV (referred to as the IC-ZCD assay).[9] These cases demonstrate important clinical aspects of coinfection and highlight the utility of a multiplex diagnostic for these viruses.

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CASE REPORTS

Case 1. In February, a 43-year-old male was hospitalized for surgical repair of nonunion of a femur fracture that had occurred 6 months earlier. The patient was started on antibiotic therapy (vancomycin and ciprofloxacin) after surgery, which was continued until discharge. The patient did not receive any blood products during his surgery. On postoperative day 5, he developed a fever, cough, and pruritic rash. Additional complaints included sore throat and joint pain predominantly involving his left knee. His maximum temperature was 39.0°C, but other vital signs were within normal limits. Physical examination revealed bilateral conjunctivitis and maculopapular rash involving his chest and back. Results of routine laboratory studies are shown in Table 1.

A serum sample, obtained on the 9th day of symptoms (postoperative day 14), was tested for ZIKV, CHIKV, and DENV using the IC-ZCD assay. The IC-ZCD assay is an internally controlled, real-time RT-PCR for the detection and differentiation of ZIKV, CHIKV, and DENV. The assay was performed as described,[9] with the inclusion of RNase P as internal control. Full methodologic detail is provided in the Supplemental Information. Serum tested positive for ZIKV and CHIKV but negative for DENV RNA. A second serum sample, collected on the 12th day of symptoms (postoperative day 17), also tested positive for ZIKV and CHIKV RNA. After resolution of his symptoms, the patient was discharged home on postoperative day 27.

Case 2. In late February, a 43-year-old woman presented for outpatient laboratory testing with 3 days of fever, headache, and diffuse myalgia. She lived in the United States, and had traveled to Ecuador 2 weeks before symptom onset to undergo assisted reproductive treatment. At the time of her visit, she was in no acute distress and had mild bilateral conjunctivitis. She denied skin rash or arthralgias. Her physical examination was unremarkable. Routine laboratory tests were not performed.

Her serum tested positive for ZIKV and CHIKV using the IC-ZCD assay. A second sample was obtained 2 days later (on the 5th day of symptoms). This again tested positive for ZIKV and CHIKV. However, C_t values in the second sample were 4.09 cycles lower for ZIKV (32.84 versus 36.93) and

TABLE 1
Results of laboratory studies performed on whole blood, serum, or plasma at presentation for Cases 1 and 3

Laboratory test	Case 1	Case 3	Normal range
White blood cell count, 10^3 cells/μL	5.46	9.7	4.5–10.4
Hemoglobin, g/dL	12.8	11.7	12.0–15.5
Platelet count, 10^3 cells/μL	398	207	150–450
Creatinine, mg/dL	1	0.8	0.6–1.2
Glucose, mg/dL	93	155	70–100
Aspartate transaminase, units/L	54	46	10–40
Alanine transaminase, units/L	43	31	7–56
Human immunodeficiency virus			
Fourth-generation screen	Not reactive	Not reactive	Not reactive
Quantitative RT-PCR	Not detected	Not detected	Not detected

RT-PCR=reverse transcription polymerase chain reaction. Case 2 did not have routine laboratory testing performed.

3.83 cycles lower for CHIKV (31.91 versus 35.74), consistent with ~10-fold increase in viremia for each virus.[9] A third serum sample, drawn 10 days after the first sample (day 13 of illness), remained positive for both pathogens. The patient decided not to undergo planned fertility treatment; her symptoms resolved over 7 days.

Case 3. In March, a 57-year-old female with a past medical history significant only for hyperthyroidism was admitted with severe neurologic symptoms. Her illness had begun 11 days earlier with fever, headache, and lumbar back pain. Five days later, she developed paresthesias in her hands, feet, and face, and her neurologic symptoms progressed over 2 days to quadriparesis and facial paralysis. On presentation, the patient was noted to have loss of deep tendon reflexes, and a diagnosis of GBS was made. She was admitted to the intensive care unit for treatment. Electromyography confirmed the diagnosis of GBS. Laboratory test results are shown in Table 1.

On hospital day 3, serum and cerebrospinal fluid (CSF) were sent to the laboratory for testing using the IC-ZCD assay. Both serum and CSF tested positive for ZIKV and CHIKV and negative for DENV. CSF was clear with a white blood cell count of 3/μL (67% neutrophils and 33% lymphocytes), protein of 120.2 mg/dL, and glucose of 57.1 mg/dL. For additional CSF test results, see Supplemental Information. Serum and urine samples obtained on hospital days 1 and 2 (four additional samples) were tested retrospectively. One serum and both urine samples tested positive for ZIKV; all samples tested positive for CHIKV but negative for DENV. The patient was treated with plasmapheresis. Her symptoms improved, and she was discharged home on hospital day 10.

CONCLUSIONS

We report three cases of ZIKV–CHIKV coinfection detected over a span of 2 months at the Hospital Luis Vernaza in Guayaquil, Ecuador. These cases likely resulted from mosquito-borne infections with both viruses, as none of our patients had other potential modes of infection such as receipt of blood products. Despite the cocirculation of these viruses throughout the tropical Western Hemisphere, few confirmed cases of ZIKV coinfection have been described in the literature to date. Clinically, reported coinfections could not be differentiated from monoinfections caused by ZIKV, CHIKV, and/or DENV.[7,8] In this respect, our findings are consistent with published cases and highlight the utility of a multiplex diagnostic for these viruses.

Confirmation of ZIKV–CHIKV coinfections in this series relied on the use of the IC-ZCD assay, which is a previously validated assay that detects and differentiates ZIKV, CHIKV, and DENV in clinical samples.[9] In early 2016, ZIKV, CHIKV, and DENV were circulating in Guayaquil, which is located in the coastal Guayas Province of Ecuador and has a tropical climate. During the time that these cases were detected, infections with each virus were detected at the Hospital Luis Vernaza, including monoinfections with ZIKV (N=3) and CHIKV (N=8). To ensure the accuracy of IC-ZCD assay interpretation, a color compensation file was also created. This eliminated cross-talk between channels, even when the assay was tested with quantitated standards at concentrations ~1,000-fold higher than concentrations observed in clinical samples from these three patients (see Supplemental Information).

Patients in our series had prolonged ZIKV viremia, with RNA detectable in serum until at least day 12 after symptom onset. This includes Case 2, who developed a relatively mild illness despite ZIKV–CHIKV coinfection. These data are consistent with recent reports of prolonged viremia in two returning travelers, including a pregnant woman who had ZIKV RNA detected in serum samples collected 5 weeks apart.[10,11] Such cases, all from the Americas, differ from data reported after outbreaks on Yap Island and in French Polynesia, where the majority of ZIKV RNA–positive samples were collected on or before day 5 of illness.[12,13] The finding of prolonged ZIKV viremia may be important for virus transmission, given the relatively low-level viremia detected in most cases.[9]

Cases presented here demonstrate additional interesting aspects of ZIKV–CHIKV coinfections. Case 1 developed fevers 5 days after admission for an orthopedic procedure, and 9 days after symptom onset, he was diagnosed with a ZIKV–CHIKV coinfection. This case demonstrates that acute arboviral infections can present to attention after hospital admission and confound the workup for a hospital-acquired cause of fever. In Case 3, ZIKV RNA was detected in CSF, which has rarely been reported in cases of GBS.[14] In particular, findings in Case 3 differ from reports of ZIKV detection in cases of GBS associated with ZIKV monoinfection in French Polynesia. In that series, 0/41 patients were positive for ZIKV RNA in CSF.[4]

In conclusion, the cases presented here demonstrate the varied clinical presentation of ZIKV–CHIKV coinfections as well as the importance of multiplexed arboviral testing for accurate epidemiologic surveillance and the design and interpretation of future clinical trials.

Received April 25, 2016. Accepted for publication June 6, 2016.

Published online July 11, 2016.

Note: Supplemental information appears at www.ajtmh.org.

Acknowledgments: We would like to thank the administration and staff at the Hospital Luis Vernaza, and in particular, the Molecular Diagnostics Laboratory. Patent applications or provisional patent applications have been filed that cover the ZCD multiplex assay and the primers and probes described in this article (Jesse J. Waggoner and Benjamin A. Pinsky, Stanford University).

Financial support: This research was supported by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) grant K08AI110528 (Jesse J. Waggoner) and the Robert E. Shope International Fellowship in Infectious Diseases from the American Society of Tropical Medicine and Hygiene.

Disclaimer: The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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