Zika Virus–Associated Cerebellitis with Complete Clinical Recovery

Mónica R. Pachar,^{1†} Dimelza Araújo,^{2†} Nathan D. Gundacker,³ Marixel Suárez,¹ José Antonio Suárez,² Brechla Moreno,² Sandra López-Vergès,^{2*} and Ana B. Araújo^{1*}

¹Hospital Santo Tomas, Panama City, Panama; ²Gorgas Memorial Institute of Health Studies, Panama City, Panama; ³Medical College of Wisconsin, Milwaukee, Wisconsin

Abstract. Zika virus (ZIKV) was first detected in the Americas in Brazil in 2015, with a rapid spread to surrounding countries. In Panama, the outbreak began in November 2015 in an indigenous community located on the Caribbean side of the country. Zika virus is typically associated with a diffuse rash, fever, and conjunctivitis. It can rarely cause neurologic manifestations, most commonly microcephaly and Guillain-Barré syndrome. Encephalitis and acute encephalomyelitis are known complications, but ZIKV-associated cerebellitis has yet to be reported in the literature. Herein, we report a case of cerebellitis in a patient infected with ZIKV. This patient developed severe frontal headache and vertigo on the third day of illness, and dysarthria and ataxia on the fifth day. After 1 week of hospitalization, the patient completely recovered. The laboratory serological diagnosis was complicated because of the detection of antibodies against dengue, suggesting a secondary flavivirus infection.

INTRODUCTION

Zika (ZIKV), dengue (DENV), and chikungunya (CHIKV) are arboviruses with similar clinical manifestations that primarily use mosquito vectors (*Aedes aegypti* and *Aedes albopictus*), whereas ZIKV is also sexually transmitted.^{1,2} Zika virus is a flavivirus, family Flaviviridae, that was first detected in the Americas in 2015.^{2,3} The first 50 reported ZIKV-confirmed cases in Panama occurred in an indigenous community located in the Guna Yala region on the Caribbean side close to Colombia in November 2015. During this time, DENV and CHIKV were co-circulating in the region.⁴ In 2016, there were 771 ZIKV-, 3,327 DENV-, and 11 CHIKV-confirmed cases.⁵ Zika virus typically manifests as a diffuse rash, fever, and conjunctivitis. It can cause congenital microcephaly and Guillain-Barré syndrome (GBS); however, other neurologic manifestations such as encephalitis and acute encephalomyelitis have also been reported.⁶ The neurotropism of ZIKV has been described since 1950; however, the medical significance of this was not obvious until the 2015 introduction of ZIKV into the Americas, when an increase in both neonatal microcephaly and GBS occurred.^{7–9} To our knowledge, cerebellitis associated with ZIKV infection or the immune response to ZIKV has not been described. We report a case of cerebellitis in a patient infected with ZIKV with previous DENV infection.

CASE

A 34-year-old female from the Guna Yala region, with no past medical history, developed high fever, followed by a pruritic macular rash. On the third day of illness, she developed severe frontal headache and subsequently developed vertigo. She presented to her local health department in early February 2016, where a clinical diagnosis of dengue or Zika fever was made. She then developed dysarthria and ataxia on day 5 and was transferred to Hospital Santo Tomas in Panama City for further management. On admission, she presented with headache, difficulty walking and talking, a macular rash, and dizziness. On examination, she was alert and oriented with normal cardiopulmonary and

abdominal examinations; however, her neurological examination revealed dysarthria, dysdiadochokinesia, positive Babinski sign on the left, unstable gait, and a positive Romberg sign.

IMAGES

A non-contrast computed tomography scan was obtained on admission and was unrevealing, as was cerebral magnetic resonance imaging (Figure 1). An electroencephalogram was also performed on hospital day 7, but it was unrevealing as the patient had improved at the time of the test.

LABORATORY RESULTS

Laboratory tests performed on admission (day 5 of symptoms) revealed leukocyte count of 6.9 k/uL, hemoglobin of 11.5 g/dL, and platelets of 277 k/uL. Creatinine was normal at 0.7 mg/dL, sodium was 142 mmol/L, lactate dehydrogenase was elevated at 528 U/L, and liver function tests were normal. Urinalysis was normal. Pregnancy test was negative. Cerebrospinal fluid (CSF) analysis revealed 12 leukocytes (83% polymorphonuclear leukocytes), glucose of 50 mg/dL, and protein of 116 mg/dL. Cerebrospinal fluid Gram stain and bacterial, fungal, and mycobacterial culture were negative, and blood cultures were also negative for growth. Her serum was positive for DENV non-structural protein 1 (NS1) antigen, immunoglobulin G (IgG), and immunoglobulin M (IgM) antibodies against DENV using a rapid chromatography test (SD Bioline Dengue Duo[®]; Standard Diagnostics, Abbott, US) (Table 1); however, this sample was not sent for quantitative reverse transcription–polymerase chain reaction (qRT-PCR) or viral isolation.

On day 8, ZIKV RNA^{7,8} was detected by qRT-PCR in serum, and both detected and cultured from urine on day 9. The CSF from day 12 induced cytopathic effect on Vero cells even though the viral RNA was not detected (Table 1). Dengue virus, CHIKV, alphavirus, and phlebovirus molecular tests were negative in all samples. To confirm the hospital results detecting DENV NS1 antigen and antibodies against DENV on day 5, we analyzed subsequent sera samples using the same chromatography test and enzyme-linked immunosorbent assay (ELISA) kits specific for DENV NS1, IgM, and secondary IgG (Panbio, Abbott, US), as well as for DENV memory IgG (FOCUS Diagnostics, DiaSorin, CA). Nonstructural protein 1 antigen was not detected in sera at days 8

* Address correspondence to Sandra López-Vergès, Gorgas Memorial Institute of Health Studies, Calle 36 Este, Panama City, Panama, E-mail: slopez@gorgas.gob.pa or Ana B. Araújo, Hospital Santo Tomas, Calle 37 Este, Panama City, Panama, E-mail: anabelenarauz@gmail.com.

† These authors contributed equally to this work.

FIGURE 1. Cerebral magnetic resonance imaging of the patient at hospital admission. (A) Axial T2W FLAIR. Bilateral hyperintense cortical lesions, suggestive of chronic small vessel ischemic disease. Normal gray matter differentiation. (B) Axial T1W C+. Normal enhancement. (C) Axial T1 W C+. Normal cerebellar vermis and hemispheres.

and 12; however, IgM and IgG were positive for days 8, 12, and 34 using the chromatography test but only at day 34 using the ELISA kits. We also looked for IgM against ZIKV (CDC Mac ELISA), and the test was positive for day 34 sera sample (Table 1). Sera from days 8, 12, 34, and 657 postinfection were tested for neutralizing antibodies against ZIKV using plaque reduction neutralization test, and these samples were positive with high titers for days 8, 12, and 34 that decreased at day 657. Plaque reduction neutralization test for DENV-1 and DENV-2 were also performed with these samples, and the titers were high for DENV-2 and low for DENV-1 (Table 1).

FOLLOW-UP

The patient continued to have dysarthria and difficulty walking but improved after 1 week of hospitalization. On discharge, her positive Babinski and Romberg signs had resolved and her

gait had returned to baseline. She was evaluated in December 2017, 657 days after her symptoms began. She was asymptomatic with a normal neurologic examination.

DISCUSSION

The non-congenital neurological complications associated with ZIKV American strain include encephalitis, acute disseminated encephalomyelitis, and GBS.¹⁰ Unlike African strains, the Asian and American ZIKV strains share a glycosylation site for E protein that has been proposed to mediate neurotropism.^{7–9}

The neurological symptoms and physical examination of our patient suggested cerebellitis.¹¹ Clinically, cerebellitis causes aphasia, sensory alterations, and gait abnormalities. Laboratory examinations and imaging are frequently normal in cerebellitis. The exact pathogenic mechanism of cerebellitis is unknown and

TABLE 1
Serological and virological data of a case of cerebellitis associated with ZIKV infection

Date of sample collection: days after symptoms onset	5 days	8 days	9 days	12 days	12 days	34 days	657 days
Type of sample	Serum	Serum	Urine	Serum	CSF	Serum	Serum
ZIKV qRT-PCR (CDC)	ND	Positive	Positive	Negative	Negative	NA	NA
DENV qRT-PCR (CDC)	ND	Negative	Negative	Negative	Negative	NA	NA
Generic RT-PCR for alphaviruses and phleboviruses	ND	Negative	Negative	Negative	Negative	NA	NA
Viral isolation	ND	Negative	Positive, ZIKV	Negative	Positive, ZIKV	NA	NA
DENV NS1 (ELISA PanBio)	ND	Negative	NA	Negative	Negative	NA	NA
DENV NS1 (RDT; Standard Diagnostics)	Positive	Negative	NA	Negative	Negative	NA	NA
ZIKV IgM ELISA (CDC)	ND	Negative	NA	Negative	Negative	Positive	NA
DENV IgM ELISA (Panbio)	ND	Negative	NA	Negative	Negative	Positive	NA
DENV IgM (RDT; Standard Diagnostics)	Positive	Positive	NA	Positive	NA	Positive	NA
DENV IgG ELISA (Panbio)	ND	Negative	NA	Negative	Negative	Positive	NA
DENV IgG (RDT; Standard Diagnostics)	Positive	Positive	NA	Positive	NA	Positive	NA
CHIKV IgM ELISA (IBL-International)	ND	Negative	NA	Negative	ND	Negative	NA
ZIKV-neutralizing antibodies—PRNT	ND	Positive > 1,280	NA	Positive > 1,280	NA	Positive > 1,280	Positive 320
DENV-2-neutralizing antibodies—PRNT	ND	Positive > 1,280	NA	Positive > 1,280	NA	Positive > 1,280	Positive 640
DENV-1-neutralizing antibodies—PRNT	ND	Positive 320	NA	Positive 160	NA	Positive 160	Positive 20

CHIKV = chikungunya virus; CSF = cerebrospinal fluid; DENV = dengue virus; ELISA = enzyme-linked immunosorbent assay; NA = not applicable; ND = not done; NS1 = nonstructural protein 1; PRNT = plaque reduction neutralization test; qRT-PCR = quantitative reverse transcription-polymerase chain reaction; RDT = rapid diagnostic test; ZIKV = Zika virus.

most patients will completely recover with supportive care.¹² Approximately 0.5% to 6% of patients with symptomatic DENV have neurologic complications; however, cerebellitis is rare and our literature search found only four cases associated with DENV and no cases were found associated with ZIKV.¹²

The molecular tests indicated active ZIKV infection. Reverse transcription polymerase chain reaction (RT-PCR) for ZIKV in sera and urine is highly specific,^{13,14} suggesting an association between ZIKV infection and the observed neurologic symptoms. It is unclear if the cerebellitis described was caused by the ZIKV itself or by the immune response induced by the infection. Serological tests suggested either coinfection (ZIKV/DENV), cross-reactivity between antibodies against DENV and ZIKV, or current ZIKV infection in a patient with a history of DENV where the antibody response behaves as a secondary flavivirus infection.¹⁵ The contradictory results between chromatography test and the ELISA kits for the detection of DENV IgM and IgG suggest a difference in sensitivity and specificity between the tests. Previous studies have suggested that ELISA kits are relatively more specific.^{10,16,17} The titration of neutralizing antibodies for ZIKV, DENV-1, and DENV-2 showed high titers for ZIKV and DENV-2 antibodies and lower titers for DENV-1 (Table 1). This suggests a coinfection (ZIKV/DENV-2) or a memory DENV-2 response because of probable previous DENV-2 infection and cross-reactivity with DENV-1.

Neurologic symptoms began at day 5, whereas ZIKV was detected in serum and in the urine at days 8 and 9, respectively, whereas ZIKV-neutralizing antibodies were detected at day 8; this suggests that the symptoms could be caused by both the virus and the immune response as described previously.^{18,19} As DENV was not detected by qRT-PCR in any of the analyzed samples, it is probable that the patient had only ZIKV infection, and that the positive detection of dengue NS1 antigen by rapid chromatography test on day 5 sera was due to cross-reactivity between DENV and ZIKV antibodies²⁰; however, a dual infection cannot be totally excluded as no samples before day 8 were received for molecular testing and viral isolation. The similarity of clinical symptoms and the cross-reactivity between antibodies against DENV and ZIKV (along with other flaviviruses) highlights the importance of acutely obtained samples (i.e., less than 5 days from the onset of symptoms) for a confirmed viral diagnosis of these viruses within countries where they are co-circulating.

The neurotropism of ZIKV is well documented and this case demonstrates that the neurologic presentation of ZIKV infection is a spectrum ranging from encephalitis to milder neurological complications, such as cerebellitis.

Received March 26, 2018. Accepted for publication July 24, 2018.

Published online September 24, 2018.

Acknowledgments: We thank Jack Martinez from Guna Yala region and all our colleagues from the Microbiology laboratory, Departments of Infectious Diseases, Neurology, and Epidemiology from Hospital Santo Tomas (HST). We thank all our colleagues from the Department of Research in Virology and Biotechnology, and the Immunovirology Section, Central Reference Laboratory, from ICGES. S. L. V. is a member of the Sistema Nacional de Investigación (SNI) from SENACYT, Panama. We would also like to show our gratitude to our patient and her family, for their agreement for this publication and their collaboration during the clinical approach.

Financial support: This work has been carried out with management funds of HST and ICGES, as well as MEF. project 09044.051 (S. L. V.).

Authors' addresses: Mónica R. Pachar, Maríxcel Suárez, and Ana B. Araúz, Hospital Santo Tomas, Infectious Diseases, Panama City,

Panama, E-mails: dra.pachar@hotmail.com, marixcel@gmail.com, and anabelenarauz@gmail.com. Dimelza Araúz, Brechla Moreno, and Sandra López-Vergès, Department of Research in Virology and Biotechnology, Gorgas Memorial Institute of Health Studies, Panama City, Panama, E-mails: darauz@gorgas.gob.pa, brechla@yahoo.es, and slopez@gorgas.gob.pa. José Antonio Suarez, Clinical Research Unit, Gorgas Memorial Institute of Health Studies, Panama City, Panama, E-mail: jsuarez@gorgas.gob.pa. Nathan D. Gundacker, Infectious Diseases, UAB Hospital, Birmingham, AL, E-mail: ndgundacker@gmail.com.

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