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Biphasic Zika Illness With Rash and Joint Pain

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During the current Zika virus (ZIKV) outbreak, acute symptomatic ZIKV infection in adults appears to be a mild-to-moderate, self-limited illness. We present a case of ZIKV rash illness that improved and then relapsed without repeat exposure to ZIKV. Clinicians should be alert for relapses in patients with ZIKV infection.

Keywords. joint pains; rash; relapse; Zika illness.

Zika virus (ZIKV) is a member of the Flaviviridae family and is primarily transmitted by Aedes mosquitoes to humans [1]. There were explosive outbreaks of ZIKV infections in the Americas and the islands of the Caribbean Sea in 2016. In the continental United States, as of May 31, 2017, 4952 travel-associated cases of ZIKV infection have been reported [2]. A smaller number of autochthonous cases (n = 224) in Florida and Texas have occurred since July 2016 [2]. Symptomatic ZIKV infection in healthy people is typically described as a self-limited illness with fever, rash, conjunctivitis, arthralgia, myalgia, and headache [1]. The 2 most serious complications of ZIKV infection include Congenital Zika Syndrome in an infected fetus and neurological complications such as Guillain-Barré syndrome (GBS) in adults [1, 3, 4]. In this study, we describe a case of acute ZIKV infection in an adult that evolved into a biphasic illness.

CASE PRESENTATION

In September 2016, a 60-year-old man presented to his primary care doctor with 4 days of fatigue, subjective fever, chills, dull headache, rash, muscle pains, red itchy eyes, abdominal pain, and burning pain with urination 3 days after returning from a vacation in Miami, Florida. He also reported swelling and pain in both hands and had moderate joint pain of both hips and knees. These symptoms interfered with his daily activities and he remained bed bound for 3 days. On examination, he had normal vital signs, bilateral conjunctival injection, erythema of nares, tympanic membranes and pharynx, enlarged bilateral posterior auricular nodes, and a generalized erythematous papular rash (worst on feet and ankles), but no joint effusions. His range of motion was limited in his hands due to swelling (Figure 1A and B) and pain in his fingers.

Over the next 2 weeks, most of the patient’s symptoms resolved except for mild fatigue, residual joint discomfort, and fading conjunctivitis. Four weeks after the onset of initial symptoms, he returned to our clinic with relapse of generalized erythematous papular rash, worsening of conjunctival injection, desquamation on bilateral palms, exacerbation of pain in hip joints, and swelling and pain in hands (Figure 1C). These symptoms were milder than that of the initial presentation. All of these recurrent symptoms gradually resolved over 2 weeks (6 weeks after initial presentation).

His past medical history is notable for presumed nonalcoholic steatohepatitis, thrombocytopenia of unknown etiology, hypertension, obesity, and obstructive sleep apnea. Medications include alprazolam (as needed for sleep) and olmesartan medoxomil/hydrochlorothiazide for hypertension. He consumes moderate amounts of alcohol and is a long-time cigar smoker. The patient was originally from the French Basque Country, served in the French military, and recalls receipt of a yellow fever virus (YFV) vaccine at least 25 years prior. He had an extensive travel history to areas endemic for dengue. He has been residing in the United States for more than 17 years. He traveled to Miami with family members and recalled mosquito bites. A 35-year-old male family member who resided in the same area of Miami had a similar rash illness in the same time frame as our patient, and he was also confirmed by molecular testing to have acute ZIKV infection.

At initial presentation, 5 days after symptom onset, clinical laboratory studies showed normal white blood cell count and differential, platelets 74,000/µL (his usual level was 80,000/µL; normal range 140–400 thousand/µL), normal creatinine, normal urinalysis, and negative hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus
fourth-generation Ag/Ab test. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 128 (range 10–35 U/L) and 171 (range 9–46 U/L), respectively, compared with his baseline AST/ALT of 67/80. Zika virus infection was diagnosed by his primary physician with a positive qualitative ZIKV ribonucleic acid (RNA) real-time reverse-transcription polymerase chain reaction (RT-PCR) in urine and serum at a local laboratory (Quest Diagnostics), 5 days postsymptom onset (Table 1); additional sample from this time point was not available for further testing. Dengue virus (DENV) RNA was not detected in subsequent samples; chikungunya virus (CHKV) and West Nile virus (WNV) PCRs were not performed.

The patient provided informed consent to join a natural history study of Zika virus infection (NIH/NIAID/DMID 16-0017), which was approved by Emory University Institutional Review Board. Signs and symptoms, clinical laboratory tests, and virologic and immunologic assays were performed at time points designated as days post onset of symptoms (DPO). Specimens were tested for ZIKV using quantitative real-time RT-PCR assay [5]. On DPOs 13, 34, and 76, his serum, urine, and saliva were negative for ZIKV RNA, but whole blood was positive on all 3 days at a low level (Table 1). His semen contained ZIKV RNA on DPO 34 but was negative on DPO 76. Serologic testing for anti-ZIKV immunoglobulin (Ig)M (monoclonal antibody capture enzyme-linked immunosorbent assay) was positive on DPO 13 and remained positive on DPO 76 [6]. Neutralizing antibody titer (by 50% focus reduction neutralization test or FRNT_{50}) for ZIKV peaked on DPO 13 (3028), and DENV 1–4 titers were also positive (1411–2419). ELISpot assays for anti-body-secreting cells against ZIKV, DENV 1–4, WNV, and YFV were negative on DPO 13. On DPOs 13 and 34, antiviral CD4+ and CD8+ T cells against peptides from multiple ZIKV proteins were present (Table 2).

**DISCUSSION**

Zika illness is generally described as a self-limited illness that typically resolves within 1 to 2 weeks after symptom onset [1]. The patient presented here acquired ZIKV infection via autochthonous transmission in the continental United States. He had an interesting biphasic Zika illness with initial improvement and near resolution of signs and symptoms and then a relapse of rash and worsening joint pains and conjunctivitis 4 weeks after acute infection. Concurrent infection with other arboviruses such as CHKV and DENV have been reported in ZIKV outbreaks [7]. However, it is highly unlikely that our patient had either of these as concurrent infections. Dengue virus real-time RT-PCR of whole blood samples collected on DPOs 13, 34, and 76 were negative [8], and only 2 cases of locally acquired dengue infection were reported in Florida in 2016 [9]. It is also unlikely that he had concurrent infection with CHKV because no locally
Our patient had pre-existing immunity to DENV, which is consistent with his extensive travel to dengue-endemic areas. High-neutralizing antibody titers against DENV during early ZIKV infection in our patient is consistent with a secondary flavivirus infection [5,6]. In this patient, the roles of pre-existing flavivirus immunity (from both past DENV infection and YFV vaccination) and its contribution to the biphasic illness remain unknown.

**CONCLUSIONS**

Zika virus illness can present as a biphasic illness with relapse of symptoms after initial improvement or resolution. The etiology of a biphasic presentation remains unclear but could be due to persistent viremia or viral persistence in so-called “sanctuary sites” and could be an indicator of more severe illness.

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**References**


