Pericarditis Associated With Acute Zika Virus Infection in a Returning Traveler.

Jesse Waggoner, Emory University
Nadine Rouphael, Emory University
Yongxian Xu, Emory University
Muktha Natrajan, Emory University
Lilin Lai, Emory University
Shital M. Patel, Baylor College of Medicine
Rebecca Levit, Emory University
Srilatha Edupuganti, Emory University
Mark Mulligan, Emory University

Journal Title: Open Forum Infectious Diseases
Volume: Volume 4, Number 2
Publisher: Oxford University Press (OUP) | 2017-05-18, Pages ofx103-ofx103
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1093/ofid/ofx103
Permanent URL: https://pid.emory.edu/ark:/25593/s41r6

Final published version: http://dx.doi.org/10.1093/ofid/ofx103

Copyright information:
© 2017 Infectious Diseases Society of America
This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Accessed September 15, 2017 10:21 AM EDT
Pericarditis Associated With Acute Zika Virus Infection in a Returning Traveler

Jesse J. Waggoner,1 Nadine Rouphael,1,3 Yongxian Xu,1,3 Muktha Natrajan,1,3 Lilin Lai,1,3 Shital M. Patel,4 Rebeca D. Levit,2 Srilatha Edupuganti,1,3 and Mark J. Mulligan1,3

Divisions of Infectious Diseases and Cardiology, Department of Medicine, School of Medicine, Emory University, Atlanta, Georgia; The Hope Clinic of the Emory Vaccine Center, Emory University, Decatur, Georgia; and Baylor College of Medicine, Houston, Texas

Despite the widespread outbreak, few cases of Zika virus associated with cardiac manifestations have been described. We present a case of pericarditis in the setting of an acute, symptomatic Zika virus infection in a traveler returning from St. Thomas. Clinicians should be alert for this potential complication of Zika virus infection.

Keywords. pericarditis; Zika virus.

Zika virus (ZIKV) is a member of the Flaviviridae family and is primarily transmitted to humans by Aedes mosquitoes [1]. The World Health Organization declared ZIKV as a Public Health Emergency of International Concern in February 2016, and, currently, there are ZIKV outbreaks in the Americas as well as islands of the Caribbean Sea and Pacific Ocean. In the United States, most cases have occurred among travelers returning from locations in the Western Hemisphere. Symptomatic ZIKV infections in adults are typically described as a mild illness with some combination of fever, rash, conjunctivitis, arthralgia, myalgia, and/or headache. However, ZIKV infections have also been associated with severe complications typically affecting the nervous system [2–4]. In this study, we describe a case of acute ZIKV infection presenting with pericarditis.

CASE PRESENTATION

In October 2016, a 45-year-old woman presented to our clinic with 4 days of subjective fever, chest pain, rash, and joint pain after returning from St. Thomas in the United States Virgin Islands. She had no prior flavivirus exposure based on immunization history and previous travel. She visited the island for 11 days, and on the day of her return, she noted a small, pruritic rash on her left arm. During the flight home, she noted that the rash was spreading, and her eyes felt swollen. The patient also experienced an episode of stabbing, substernal chest pain that radiated around her right side to her scapula. The pain improved after she stood and walked in the aisle of the plane. On the day before her presentation in clinic, she had 2 additional episodes of transient chest pain, both occurred while sitting and improved with walking.

On St. Thomas, the patient stayed in a friend’s guest house, which had no air conditioning or running water. There were screens on the windows but visible holes around the sides of the screens. The patient reported having many mosquito bites despite using insect repellent. Her friend’s son had also recently been diagnosed with Zika. The patient was not sexually active during her trip.

Her past medical history included mitral valve prolapse, irregular menses, and a congenital single kidney. Her family history was significant for cardiovascular disease. The patient had smoked cigarettes for over 20 years and smoked half a pack a day at the time of her visit. She walked approximately 1 mile a day but had not been able to exercise after her return. She was not on any prescription medications but took cranberry extract, glucosamine-chondroitin, fish oil, and a multivitamin daily.

On physical exam, 4 days after symptom onset, the patient had a temperature of 36.6°C. Her blood pressure was 155/95, heart rate 134 beats per minute, respiratory rate 20 breaths per minute, and oxygen saturations 99% on room air. She was in no acute distress. She had a soft, non-tender abdomen with normal bowel sounds. Her lungs were clear without rales or cracks. She had 2+ distal pulses and nonpitting edema of her ankles. There was no evidence of synovitis, but skin exam revealed a diffuse, predominantly papular rash over her upper and lower extremities. During the flight home, she noted that the rash was spreading, and her eyes felt swollen. The patient also experienced an episode of stabbing, substernal chest pain that radiated around her right side to her scapula. The pain improved after she stood and walked in the aisle of the plane. On the day before her presentation in clinic, she had 2 additional episodes of transient chest pain, both occurred while sitting and improved with walking.

Despite the widespread outbreak, few cases of Zika virus associated with cardiac manifestations have been described. We present a case of pericarditis in the setting of an acute, symptomatic Zika virus infection in a traveler returning from St. Thomas. Clinicians should be alert for this potential complication of Zika virus infection.

**CASE PRESENTATION**

In October 2016, a 45-year-old woman presented to our clinic with 4 days of subjective fever, chest pain, rash, and joint pain after returning from St. Thomas in the United States Virgin Islands. She had no prior flavivirus exposure based on immunization history and previous travel. She visited the island for 11 days, and on the day of her return, she noted a small, pruritic rash on her left arm. During the flight home, she noted that the rash was spreading, and her eyes felt swollen. The patient also experienced an episode of stabbing, substernal chest pain that radiated around her right side to her scapula. The pain improved after she stood and walked in the aisle of the plane. On the day before her presentation in clinic, she had 2 additional episodes of transient chest pain, both occurred while sitting and improved with walking.

On St. Thomas, the patient stayed in a friend’s guest house, which had no air conditioning or running water. There were screens on the windows but visible holes around the sides of the screens. The patient reported having many mosquito bites despite using insect repellent. Her friend’s son had also recently been diagnosed with Zika. The patient was not sexually active during her trip.

Her past medical history included mitral valve prolapse, irregular menses, and a congenital single kidney. Her family history was significant for cardiovascular disease. The patient had smoked cigarettes for over 20 years and smoked half a pack a day at the time of her visit. She walked approximately 1 mile a day but had not been able to exercise after her return. She was not on any prescription medications but took cranberry extract, glucosamine-chondroitin, fish oil, and a multivitamin daily.

On physical exam, 4 days after symptom onset, the patient had a temperature of 36.6°C. Her blood pressure was 155/95, but other vital signs were within normal limits. Heart rate and rhythm were regular with normal heart sounds, no rubs, murmurs or gallops, and she had a non-displaced point of maximum impulse. Her jugular venous pressure was flat. The patient had 2+ distal pulses and nonpitting edema of her ankles. There was no evidence of synovitis, but skin exam revealed a diffuse, predominantly papular rash over her upper and lower extremities (Figure 1A), back, and chest. Results of routine laboratory tests were within normal limits (Table 1). Notably, the levels of creatine kinase-MB fraction (1 ng/mL; normal ≤6 ng/mL) and troponin 1 (<0.03 ng/mL; normal ≤0.04 ng/mL) were normal. Screening tests for human immunodeficiency virus and hepatitis B and C were negative. Reverse-transcription polymerase chain reactions (RT-PCRs) performed on serum were negative for dengue virus (DENV) and chikungunya virus.

Serum and urine collected at her initial visit were positive for ZIKV ribonucleic acid (RNA) using a real-time RT-PCR protocol based on assays developed by Lanciotti et al [5]. Results of serologic and cellular immunology testing for ZIKV are shown in Figure 1B–E. Serologic testing for anti-ZIKV immunoglobulin (Ig)M was negative on day 7 post-illness onset, but it was
positive on day 9 and remained detectable through day 29, which was the last time point tested. ZIKV focus reduction neutralization test (FRNT) titers similarly increased from <30 on day 7 but was positive on days 9, 15, and 29. Horizontal red dashed line indicates IgM ratio positive cutoff of ≥3. Focus reduction neutralization test (FRNT) for ZIKV (in blue) was <30 on day 7 and became positive (≥titer of 30; cutoff shown with dashed blue horizontal line); DENV-4 titer was <30 on days 7 and 9 but was positive on days 15 and 29. (C) Focus reduction neutralization test. Day 29 serum neutralized both ZIKV and DENV-4 but with a higher titer against ZIKV (1724) than DENV-4 (327), which is consistent with this ZIKV infection being an initial flavivirus infection in this patient. (D) Plasmablasts and activated CD4+ and CD8+ T cells on symptom days 9, 15, and 29. CD27+CD38+ plasmablasts (antibody-secreting B cells; solid black line) had a robust detected peak at the first time-point studied (symptom day 9) then decreased. A very strong peak in human leukocyte antigen (HLA)-DR+CD38+ activated CD8+ T cells (dashed tan line) occurred later (symptom day 15), and they were still elevated on day 29, suggesting ongoing antigenic stimulation. The HLA-DR+CD38+ CD4+ T cells (dotted black lines) had a much more modest detected peak on day 9. E) ZIKV-specific CD4+ or CD8+ T-cell responses in peripheral blood mononuclear cells from day post symptom onset (DPO) 27. The percentages of total cytokine-producing cells among all CD4+ or CD8+ T cells were determined by intracellular cytokine staining and flow cytometry; results are shown for peptide pools spanning all 10 ZIKV proteins. Results for production of 5 cytokines (interferon-γ, interleukin-2, tumor necrosis factor-α, CD107, and macrophage inflammatory protein-1β) were summed in a Boolean analysis. Percentages >0.1% (bolded in the table) were considered significantly elevated relative to healthy human controls (data not shown). The patient’s CD4+ T cells mounted their strongest DPO 27 response against the non-structural proteins NS1 and NS5. The patient’s CD8+ T cells mounted their strongest response against the structural protein E and the nonstructural proteins NS3 and NS5.
stated robust responses in the setting of this infection. The
immunologic milieu in our patient differs from that of adult
patients in whom prior flavivirus infection and/or vaccination
are common, and it also differs from the case report of myocar-
ditis, in which the individual had evidence of a previous DENV
infection [9]. Our case indicates that cardiac manifestations
may occur in flavivirus-naive individuals as well as those with
previous flavivirus exposure.

The diagnosis of pericarditis in this case was based largely
on the characteristic clinical presentation and her response to
treatment [10]. In terms of other common causes of pericar-
ditis [11], the patient was in good health, had no risk factors
for tuberculosis, did not have evidence of a connective tissue
disease, and had no recent trauma. She was up to date on can-
cer screening, had normal thyroid and kidney function testing,
and was not taking medications typically associated with per-
icarditis. Although causation cannot be proven, ZIKV is the
most likely etiologic agent in this case due to the concurrent
symptoms of pericarditis and acute Zika, along with detection
of ZIKV RNA in serum and urine samples. Diagnostic con-
firmation requires testing of pericardial fluid and/or tissue,
but because of her uncomplicated clinical course and lack of
a significant pericardial effusion, there was no indication for
pericardiocentesis. Magnetic resonance imaging could further
characterize myopericarditis, but it was not performed due to
her clinical improvement.

Pericarditis has been reported in the setting of other fla-
vivirus infections, most commonly in acute dengue [12, 13].
Although the total number of cases is small, the majority of
patients have presented between days 3 and 6 post-illness
onset with ongoing symptoms of dengue fever [12–14].
Cases include both primary and secondary DENV infections
[12], and when RT-PCR has been performed, DENV RNA is
detectable at the time of presentation [12, 14]. The clinical
history in our patient is consistent with reports of pericardi-
tis in the DENV literature as well as the case of myocarditis
associated with ZIKV [9]. Although we did observe a rise in
DENV FRNT titers, this is consistent with known cross-re-
actions between anti-ZIKV antibodies and DENV serologic
assays [1]. Dengue virus RNA was not detected in acute-
phase serum, and her anti-ZIKV FRNT titers were >4-fold
higher than the DENV titers, which is consistent with an
acute ZIKV infection.

Treatment of acute viral pericarditis is supportive and con-
sists of nonsteroidal antiinflammatory drugs (NSAIDs) and
colchicine. The addition of colchicine to conventional anti-
flammatory therapy reduces symptom persistence and risk of
recurrence [15]. Our patient responded to colchicine without
the addition of NSAIDs. Currently, there is no antiviral or vac-
cine for ZIKV, and prevention of infection is accomplished
principally through avoidance of mosquito bites in endemic
areas and barrier precautions during sexual intercourse after
infection or exposure [16].

### DISCUSSION

In this report, we describe a case of pericarditis that occurred
during an acute, symptomatic ZIKV infection. The neurologi-
cal complications of ZIKV infection have been well described
[4, 6]. Cardiac manifestations have not been commonly
observed in the setting of Congenital Zika Syndrome [7].
However, ZIKV infection has reportedly been associated with
cardiac complications such as dysrhythmias and heart failure
in Venezuelan adults [8], and a case report of myocarditis asso-
ciated with Zika in a traveler who returned to France from La
Martinique has recently been published [9]. In our patient,
clinical history and antiviral antibody testing were consistent
with an acute ZIKV infection being a primary flavivirus infec-
tion. Humoral and cell-mediated immunity assays demon-
strated robust responses in the setting of this infection. The

### Table 1. Results of Routine Laboratory Testing

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>5000/µL</td>
<td>4000–10000/µL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>14.4 g/dL</td>
<td>11.4–14.4 g/dL</td>
</tr>
<tr>
<td>Platelet count</td>
<td>230000/µL</td>
<td>150000–400000/µL</td>
</tr>
<tr>
<td>Sodium</td>
<td>135 mEq/L</td>
<td>136–144 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.9 mmol/L</td>
<td>3–6 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>102 mmol/L</td>
<td>101–111 mmol/L</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>24 mmol/L</td>
<td>22–32 mmol/L</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>9 mg/dL</td>
<td>8–25 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.85 mg/dL</td>
<td>0.4–1.0 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>88 mg/dL</td>
<td>65–110 mg/dL</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.4 mg/dL</td>
<td>&lt;1.3 mg/dL</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>34 U/L</td>
<td>5–35 U/L</td>
</tr>
<tr>
<td>Aspartic aminotransferase</td>
<td>10 U/L</td>
<td>5–35 U/L</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>62 U/L</td>
<td>40–120 U/L</td>
</tr>
<tr>
<td>Troponin I</td>
<td>&lt;0.03 ng/mL</td>
<td>≤0.04 ng/mL</td>
</tr>
<tr>
<td>Creatine kinase-MB fraction</td>
<td>1 ng/mL</td>
<td>≤6 ng/mL</td>
</tr>
</tbody>
</table>
CONCLUSIONS

In conclusion, we present a case of pericarditis in a ZIKV-infected patient. Clinicians should be aware of this presentation during the current outbreak, because it requires close follow-up and may improve quickly with medical management.

Acknowledgments

We thank the clinical staff at The Hope Clinic (Mary Bower, Sara Jo Johnson, Allison Beck, Dean Kleinhenz, and Jo Ann Sadowski) and the laboratory staff at The Hope Clinic Laboratory (Pamela Lankford-Turner, Sree Aramgam, Dongli Wang, and Vinit Karmali).

Disclaimer. The patient described in this case report provided written informed consent to participate in a natural history study of Zika virus infection (DMID 16-0017). The immunologic testing presented herein was performed as part of this ongoing study.

Financial support. This case report details a research study participant in a Zika virus natural history study funded by a National Institutes of Health/National Institute of Allergy and Infectious Diseases/Division of Microbiology and Infectious Diseases (DMID) Vaccine and Treatment Evaluation Unit (VTEU) award to Emory University (Contract No. HHSN272201300015I). Additional support was provided by the Georgia Research Alliance.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References