We report the case of a 48-year-old American traveler who presented to our clinic with diffuse rash, malaise, fatigue, fever, arthralgia, low back pain, and bilateral exudative conjunctivitis. The patient had an extensive vaccination and travel history: most notable for prior receipt of yellow fever vaccine; extensive travel or residence in areas endemic for dengue, chikungunya, and West Nile virus; and recent travel to French Polynesia. Clinical and laboratory findings were consistent with Zikavirus (ZIKV) infection. Our report highlights the need to include ZIKV in the differential diagnosis, especially in febrile patients with a rash returning from endemic areas.

Case Report

A 48-year-old previously healthy male, who resides in New York City, presented to our clinic in December 2013 with an 11-day history of diffuse rash, malaise, fatigue, fever, arthralgia, low back pain, and bilateral exudative conjunctivitis. Five weeks prior to his acute illness, he traveled to the highlands of Ecuador, Peru, and Bolivia as well to the urban areas of Chile, Easter Island, French Polynesia (Tahiti and Moorea), and Hawaii. During his travel to Moorea, French Polynesia, the patient recalled several mosquito bites despite the use of insect repellents containing 30% DEET. Within 12 hours after departing French Polynesia, he noted a pruritic erythematous rash on the posterior area of his neck. Over the next several days as the rash progressed, he developed malaise, fatigue, fever (38.8°C), marked arthralgia, low back pain, and bilateral exudative conjunctivitis. These symptoms and the fever peaked within a week of onset. The patient experienced symptomatic relief by using an over-the-counter analgesic and an oral antihistamine. By day 9, the patient’s symptoms were generally resolved with the exception of progression of the rash. Upon returning to New York, he presented to our clinic for evaluation on day 11 and he returned for follow-up on day 31. On the day 31 visit, the patient’s symptoms had fully resolved with no residual sequelae.

Over the previous 20 years, the patient had an extensive global travel history including multiple visits to areas endemic for dengue, chikungunya, yellow fever, and malaria. The patient lives in an area endemic for West Nile virus in New York. During his prior travels, he reported compliance with pre-travel health care comprising all relevant vaccines, including a yellow fever vaccination from our clinic in 1999.

Physical examination was within normal limits except for a diffuse erythematous maculopapular rash on his torso and extremities (Figure 1).

Laboratory tests revealed a normal complete blood count with differential and normal serum electrolytes and hepatic and renal profiles. Serum samples were obtained on day 11 and day 31. RT-PCR testing, recommended within 5 to 10 days of symptom presentation for viremia detection, could not be performed based on strict laboratory protocol that required sample submission by day 10. The day 11 sample revealed positive immunoglobulin M (IgM) titers for both dengue [enzyme-linked immunosorbent assay (ELISA)] and West Nile virus (ELISA and IFA). ELISA for Zika virus (ZIKV) IgM showed negative result. Day 11 IgG titers were: 1:80 (ZIKV), 1:80 (dengue virus), and reactive (West Nile virus). The day 31 sample revealed a positive ZIKV IgM titer as well as a fivefold increase in ZIKV IgG titer (1:2,560). There was no significant change in
Figure 1 Zika virus (ZIKV) erythematous maculopapular rash.

Table 1 Acute and convalescent serology

<table>
<thead>
<tr>
<th>Virus</th>
<th>Antibody</th>
<th>Day 11</th>
<th>Day 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zika</td>
<td>IGM</td>
<td>NEG</td>
<td>POS</td>
</tr>
<tr>
<td></td>
<td>IGG</td>
<td>1:80</td>
<td>1:2,560</td>
</tr>
<tr>
<td>Dengue</td>
<td>IGM</td>
<td>POS</td>
<td>POS</td>
</tr>
<tr>
<td></td>
<td>IGG</td>
<td>1:80</td>
<td>1:160</td>
</tr>
<tr>
<td>West Nile</td>
<td>IGM</td>
<td>POS</td>
<td>POS</td>
</tr>
<tr>
<td></td>
<td>IGG</td>
<td>POS</td>
<td>POS</td>
</tr>
</tbody>
</table>

the dengue virus IgG titer (1:160), and the West Nile virus IgG titer remained reactive (Table 1).

The patient’s acute clinical illness was consistent with ZIKV infection considering his recent travel to French Polynesia where a large ZIKV outbreak was occurring. Also, the fivefold increase in ZIKV titer between days 11 and 31 (1:80 vs 1:2,560, respectively) and the lack of significant change of the dengue virus or the West Nile virus titers between days 11 and 31 are supportive of the diagnosis of ZIKV infection. The presence of dengue and West Nile antibodies is most likely due to cross reactivity with ZIKV (ie, all are flaviviruses) and/or prior infection with or immunization against other flaviviruses, specifically yellow fever. This is the first published case report of ZIKV infection in a recreational American traveler.

Discussion

History and Transmission

ZIKV is a mosquito-borne RNA flavivirus of the same Flaviviridae family as that of the dengue, yellow fever, Japanese encephalitis, and West Nile viruses. The virus was first isolated in 1947 from a febrile sentinel rhesus monkey in the Zika Forest of Uganda. The geographical location of the isolate later served as the name for the virus. Well-documented human cases have been reported beginning in the 1960s. ZIKV is considered an emerging arboviral disease because of its expanding geographic distribution. ZIKV outbreaks have been reported in tropical Africa, Southeast Asia, and more recently in the Pacific Islands. Historically, ZIKV infections had been limited to sporadic cases or small-scale epidemics until 2007 when a larger epidemic was described in Yap, Micronesia. Since late 2013, an epidemic of more than 28,000 infected patients has been reported in French Polynesia, including popular vacation destinations Tahiti and Bora Bora. Recreational travel-related imported ZIKV infections have been reported in returning travelers to multiple countries including recent reports on ZIKV infections from Thailand to Germany, French Polynesia to Japan, and Indonesia to Australia. ZIKV infection has also been reported in field researchers returning from Senegal to the United States. Possible human-to-human close contact or sexual transmission was suspected when the spouse of one of the returning field researchers became infected in spite of not having traveled to an endemic zone. Two newborns tested positive for ZIKV within days of delivery during the recent French Polynesia outbreak, raising the possibility of trans-placental or perinatal ZIKV transmission. Potential for blood transfusion-associated ZIKV transmission has been demonstrated in a recent study evaluating blood donors by PCR testing during the 2013 to 2014 French Polynesian epidemic.

ZIKV is transmitted by Aedes mosquito species, most notably Aedes aegypti, Aedes albopictus, and Aedes polynesiensis. Aedes aegypti is usually found in the tropical and subtropical regions of the world, and A. albopictus is now established in many parts of Europe, especially the Mediterranean countries. In French Polynesia, A. polynesiensis is a known vector of both ZIKV and dengue, which is relevant to our case report. Reports of recently imported cases of ZIKV infection from Southeast Asia or the Pacific to Europe, Japan, and Australia highlight the risk of ZIKV emergence in parts of the world where Aedes spp. is established. A recent ZIKV genetic characterization study highlights the need for active surveillance to monitor for geographical expansion into areas where the vector may be present.

Clinical Manifestations

In humans, the ZIKV causes a disease known as Zika fever, which is generally self-limiting. Clinical manifestations can be difficult to differentiate from dengue and chikungunya infections. The most common symptoms of ZIKV infection are a maculopapular skin rash that starts on the face or trunk and becomes more diffuse, headaches, low-grade fever, arthralgias, myalgia, and conjunctivitis. The first documented case of ZIKV infection complicated by Guillian-Barre syndrome was reported from French Polynesia in early 2014. Since then, the French Polynesian health reports continue to report additional cases of Guillian-Barre syndrome that are suspected to be secondary to primary ZIKV.
ZIKV can be identified by RT-PCR to detect ZIKV RNA in patients who present with an exposure of <10 days prior by collecting acute-phase specimens. Convalescent specimens can be useful 5 days post-onset of fever by ELISA serology for the detection of specific IgM antibodies to ZIKV.\textsuperscript{10,15} Serological cross-reactivity with other flaviviruses is possible.\textsuperscript{3,4} In the absence of serological confirmation, a clinical diagnosis is warranted.

Symptomatic management with supportive care is indicated for acute cases. Prevention is achieved by vector control and insect bite precautions. \textit{Aedes} spp. is adapted for indoor and daytime biting in urban areas. They are known to breed in aquatic environments such as small puddles, open water storage containers, and plants that hold water between the leaves and stems. Insect bite precautions (during early morning and late afternoon peak biting times) and vector control should be tailored to known epidemiology. To date, there is no vaccine for the prevention of ZIKV.

\textbf{Conclusion}

Our report highlights the need to include ZIKV infection in the differential diagnosis, especially in febrile patients with a rash returning from affected areas.

\textbf{Acknowledgments}

The authors gratefully acknowledge Dr J.S. Keystone, Professor of Medicine, University of Toronto, and M.-L. Scully, MD, Director, Travel and Tropical Medicine Center, Sansum Clinic, Santa Barbara, CA, for their review, advice, and comments regarding the original manuscript, and L. Berger for his assistance in the final preparation and formatting of the Brief Communication.

\textbf{Declaration of Interests}

The authors state that they have no conflicts of interest to declare.

\textbf{References}