Chikungunya Fever from Malaysia

Kouta Yamamoto¹, Kentaro Matumoto¹, Chang-Kweng Lim², Meng Ling Moi², Akira Kotaki² and Tomohiko Takasaki²

Abstract

An adult Malaysian woman returned to Japan from Kuala Lumpur and had onset of dengue fever-like symptoms including high fever, malaise and arthritis in early January 2009. Serum obtained on the following day was tested at the National Institute of Infectious Diseases in Tokyo, where it was determined to be positive for chikungunya virus (CHIKV) RNA. IgM antibody against CHIKV was negative on January 6 and sero-converted to be positive on January 14, confirming a recent CHIKV infection. Except for arthralgia, all her symptoms resolved uneventfully within 10 days.

Key words: Chikungunya fever, travel medicine, medicine for foreigner

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Introduction

Returning travelers often present to medical facilities for evaluation with complaints of flu-like symptoms (i.e., fever and myalgia). A total of 2-3% of European and American travelers to developing countries reported fever (1). Upon return from tropical and subtropical areas, malaria and dengue fever are the diseases typically attempted to be diagnosed immediately due to the concern for adverse outcomes. However, other fever-associated vector-transmitted diseases also need to be considered to avoid delayed treatment. In January 2009, we diagnosed a traveler who returned from Malaysia as suffering from Chikungunya fever (CHIK fever); her serum sample from the acute phase of the illness to convalescent phase was investigated for viral isolation and serologic diagnosis.

Chikungunya virus (CHIKV) is an arthropod-borne RNA virus, a member of the genus Alphavirus (32 spp., Togaviridae family), which was first isolated in Tanzania in 1953. Unlike other alphaviruses causing mosquito-transmitted human joint disorders such as, O’nyong-nyong virus (central Africa), Igbo-ora virus (Ivory coast), Ross River virus (Australia, New Zealand, New Guinea and the Pacific), Barmah Forest virus (Australia), Sindbis virus (Sweden, Finland, Karelian isthmus of Russia), and Mayaro virus (Bolivia, Brazil, Peru), a number of outbreaks of infection with CHIKV have been reported over a large geographical region that includes several African countries, the Indian subcontinent, and southeast Asia. Recently CHIK fever outbreaks occurred in Kenya in 2004, followed by outbreaks on several islands in the southwest Indian Ocean, including the island of La Réunion in early 2005 which caused a large outbreak in India in 2005-07. In 2006, approximately 2 million people were estimated to be infected with CHIKV (2, 3), including more than 1,000 travelers who returned to Europe, the United States and other nonendemic areas from the regions where the outbreaks occurred (2, 4). In Japan in December 2006, two patients who had returned from travel to Sri Lanka were serologically confirmed to have recent CHIKV infection (5). In 2008-09, CHIK fever continued to spread, becoming endemic in the Indian subcontinent and Southeast Asia including the countries of Malaysia, Singapore, Indonesia and Sri Lanka. As of July 2009, 10 imported CHIK fever cases were reported in Japan. We present the case of a Malaysian woman infected with CHIK fever (6) as well as a review of the surveillance/diagnostic system of CHIK fever in Japan. We also discuss the potential introduction of CHIKV by returning travelers to nonendemic areas in Japan, where the Aedes species which may serve as a vector of CHIKV, are inhabitant.

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Table 1. Tests Results

<table>
<thead>
<tr>
<th></th>
<th>ref</th>
<th>6 Jan</th>
<th>7 Jan</th>
<th>8 Jan</th>
<th>14 Jan</th>
<th>21 Jan</th>
<th>4 Feb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Protein</td>
<td>(-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>WBC</td>
<td>3500–9100/μL</td>
<td>7050</td>
<td>5090</td>
<td>3930</td>
<td>5150</td>
<td>7790</td>
<td>5960</td>
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<tr>
<td>Neutro</td>
<td>40–70%</td>
<td>89.4</td>
<td>81.7</td>
<td>56</td>
<td>54</td>
<td>56.5</td>
<td>53</td>
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<tr>
<td>Lympho</td>
<td>20–45%</td>
<td>6.4</td>
<td>13</td>
<td>36.8</td>
<td>33</td>
<td>31.2</td>
<td>35.8</td>
</tr>
<tr>
<td>atypical lym</td>
<td></td>
<td>2</td>
<td></td>
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<td></td>
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<tr>
<td>RBC</td>
<td>378-500 x 10(4)/μL</td>
<td>496</td>
<td>478</td>
<td>496</td>
<td>479</td>
<td>458</td>
<td>454</td>
</tr>
<tr>
<td>Plt</td>
<td>13–36.9 x 10(4)/μL</td>
<td>29.4</td>
<td>28.5</td>
<td>28.8</td>
<td>43.2</td>
<td>48</td>
<td>35.4</td>
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<tr>
<td>CRP</td>
<td>0–0.5 mg/dL</td>
<td>1.86</td>
<td>6.61</td>
<td>2.88</td>
<td>0.41</td>
<td>0.93</td>
<td>0.14</td>
</tr>
<tr>
<td>GPT</td>
<td>10–34 U/L</td>
<td>24</td>
<td>41</td>
<td>16</td>
<td>11</td>
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<tr>
<td>LDH</td>
<td>119–229 U/L</td>
<td>223</td>
<td>257</td>
<td>307</td>
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<td>ALP</td>
<td>115–359 U/L</td>
<td>250</td>
<td>214</td>
<td>221</td>
<td>228</td>
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<tr>
<td>CK</td>
<td>45–153 U/L</td>
<td>73</td>
<td>56</td>
<td>43</td>
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<td></td>
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<tr>
<td>CREN</td>
<td>0.36–1.06 mg/dL</td>
<td>0.45</td>
<td>0.54</td>
<td>0.48</td>
<td>0.44</td>
<td>0.38</td>
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</tr>
</tbody>
</table>

CHIKV RT-PCR (-) +  +  -  -  -
IgM-CHIKV (-) -  -  +  +  +
P/N ratio <2.0 1.07 0.98 3.46 3.35
NT-CHIKV -  -  +  +  +
titer <10 <10 <320 x 1280
DENV RT-PCR (-) -  -  NT  NT  NT
IgM-DENV (-) -  -  -  -  -
IgG-DENV (-) +  +  +  +  +

Case Report

On January 6, 2009, a 41-year-old Malaysian woman, a resident of Kobe, Japan for 3 years, presented with dengue fever-like symptoms, including high fever, malaise and arthritis. She had recently visited Kuala Lumpur, Malaysia, from December 19, 2008 to January 3, 2009, during the rainy season. On the evening of January 5, she developed a high fever and polyarthritis, predominately in her hands, feet and ankles with her large joints less affected.

Upon presentation, she appeared fatigued, but was alert without any meningitis symptoms, diarrhea, jaundice or petechia. She denied recent exposure to poultry/ or contact with any flu patients. She stated no past history of dengue fever (DENV). Her medications included propylthiouracil, for Graves’ disease diagnosed 3 years ago.

Other laboratory tests were negative for IgM-dengue virus (Dengue Virus IgM captured ELISA, Focus Diagnostics, Cypress, CA, USA), rapid influenza antigen test, and rapid diagnostic test (Malaria Ag. Pf/Pan, SD Standard Diganostics, Inc., Korea)/microscopy smear for malaria; however, IgG-dengue virus antibody was positive (Dengue IgG indirect ELISA, Panbio Limited, QLD, Australia). Lymphocytopenia was noted early in the patient’s course, but no thrombocytopenia developed. Mild elevation of the patient’s ALT/AST was observed transiently, however she had taken NSAIDs and acetaminophen for her febrile illness. Her bilirubin level was normal. Blood culture for salmonella typhi/paratyphi was negative. Her chest radiograph was normal and an abdominal ultrasound did not demonstrate any liver abscess on January 6 and 8.

Since a positive IgG result by rapid diagnostic tests can be difficult to interpret because of extensive cross-reactions with other genus flavivirus and since the window for a positive IgM reaction to detect dengue fever is usually 5-7 days (7), the serum obtained on January 6 was submitted for PCR assay to the National Institute of Infectious Diseases in Tokyo. It was determined to positive for CHIKV RNA with a viral RNA titer of 6.7x10 (7) copies/mL in the serum. IgM antibody against CHIKV was negative on January 6 and sero-converted to be positive one week later. IgM anti-
bodies against dengue virus (DENV) were negative in both sera, and IgG antibodies against DENV were positive in both sera, indicating previous infection with DENV. Laboratory and PCR/serologic tests are shown in Table 1. Her fever lasted 6 days and peaked at 40°C. Following defervescence, a pruritic skin rash appeared on her trunk and thigh between the 6th day and 10th day after the onset. She has had persistent arthralgia.

Other family members, including her spouse and two infants, remained afebrile and healthy for 14 days after her return to Japan, although they were not tested for CHIKV.

**Discussion**

Currently, CHIK fever is not characterized as a reportable infectious disease in Japan. Diagnosis requires laboratory confirmation, including viral isolation or detection of viral RNA by PCR (acute phase), and serologic tests, i.e., IgM-CHIKV (4-90 days) (2, 8), IgG-CHIKV (15 days to years) or a four-fold rise in CHIKV neutralizing antibodies in acute phase serum and convalescent phase. Although 50 million cases of dengue fever, the most common cause of fever in tourists, are estimated worldwide, only about 70-100 imported cases are registered annually in Japan. This reported incidence in Japan might be underestimated secondary to undiagnosed cases because of lack of a practical diagnostic system. Rapid diagnostic tests, although useful as a screening tool may result in false negatives and are not available in most medical facilities. In order to diagnose these common travel-associated illnesses in Japan, where the number of cases of malaria and dengue fever is low, submission of specimens to the reference laboratories would be required by clinicians. Diagnostic tests using virological/serologic tests for CHIKV are not available commercially in Japan. As of July 2009, 10 cases of CHIKV have been confirmed in Japan (Table 2). Of these 10 cases, eight cases were diagnosed as CHIKV infection by positive IgM antibodies and neutralization antibodies, and 2 patients were diagnosed virologically by RT-PCR and viral isolation.

**Clinical Features of Chikungunya Fever**

The most commonly reported symptoms of CHIK are fever (91-100%), headache (50-70%), arthralgia (78-100%), myalgias (50-80%), and rash (36-50%) (2-4, 8-10). There are some variations in frequency and clinical features depending on the year and location of the outbreaks. The patient in this report exhibited a typical clinical course of CHIKV, which is characterized by the sudden onset of fever and arthralgia, because of intense viremia following a mosquito bite. In the present case, the titer of viral RNA was 6.7×10^7 copies/mL in the serum sample on January 6. Parela et al reported that viral loads of CHIKV are frequently above 10^9 virus copies/mL of serum (11), in comparison to dengue fever and West Nile disease in which high levels are uncommon. The incubation period for CHIK fever is usually 2-4 days (ranging from 1-12 days), with cases increasing in the rainy season similar to other mosquito-borne illness.

The word “chikungunya” is from the Makonde language of an ethnic group in southeast Tanzania and northern Mozambique; it means “bends up” and “intense joint pains”, which are hallmarks of the disease, affecting mainly the extremities, i.e., ankles, wrists, and phalanges, but also the large joints. Fever typically reaches 39-40°C with rigors and may last 2-3 days (ranging from 1-7 days). Skin eruptions characterized by pruritic maculopapular lesions on the trunk and extremities occur in 40-50% cases, and last for 2-5 days (ranging from 1-10 days). Generally, most acute-phase symptoms resolve within 7-10 days, except for joint stiffness and pain. Although it is rare in children, arthralgias may persist for several months, with a duration of 3-5 years in 10% of affected adults.

Although the present patient in our report had mildly elevated liver enzymes, a complication attributed to excess acetaminophen intake, liver failure and meningoencephalitis (in both newborns and elderly patients) is uncommon with most CHIK cases being mild and self-limited. On the island
of La Réunion (Southwest Indian Ocean), where 265,000 clinical cases/770,000 population was reported (an incidence of 34%), there were 237 deaths related to CHIKV. Most deaths were reported to occur in the older population, who had underlying comorbidities (median age 78 years) (9), although the present strain may be more virulent than previously reported and this may have caused more deaths (2, 12). Surveillance of the virus strains should be considered in order to determine their epidemiology.

**Surveillance System of CHIKV in Japan**

West Nile fever became a reportable infectious disease (4th category) in Japan in 2001 because of explosive spread of the disease throughout North America since 1999 due to the absence of immunity. Globally, the numbers of CHIK fever cases seems to be much larger than West Nile fever cases. For instance, DENV is an epidemic in 40% of the world’s population (2.5 billion people). The CDC reported nine cases of CHIK fever from 1991 to 2004, however, 37 cases were confirmed in 2006, mostly in travelers from India (4). Moreover, the virus genome analysis proposed that the recent massive outbreak in India was caused by a new variant (2, 3, 11-13). This mutation occurred in the E1 envelope gene (A226V), which could be related to an enhanced ability of the virus to infect mosquito species and perhaps even the severity of the illness associated with human infection.

Over the last decade, the number of Japanese traveling overseas and also foreign visitors to Japan has been significantly increasing, consisting of 17.4 million overseas Japanese (367,567 people visited Malaysia), 7.3 million foreign tourists visited Japan (including 100,890 Malaysian), 1.08 million Japanese live in foreign countries (26.11% living in Asia and 0.5% in Africa, 10,231 peoples living in Malaysia), and there were 2 million foreign residents in Japan (18.2% were Asians other than Korean and Chinese and 0.5% are Africans) in 2006 (14, 15). The conspicuous recent trend of tourism in Japan has a marked increase in both trade and travel between Japan and many southeast/south Asian countries where CHIKV and DENV are endemic.

Two vectors, i.e., *Ae aegypti* and *Ae albopictus*, transmit CHIK virus. The latter, though an inefficient second vector of DENV, can also transmit a variety of viruses and is distributed worldwide. It previously was a native species to Southeast Asia, however, this mosquito virus continues to spread into many regions through both increasing international trade and global warming (2, 3). Furthermore, *Ae. albopictus* appears to be successfully adapting to cooler regions, because of the adapted tolerability of eggs against dryness.

Recently, several issued reports have warned that the increased travelers/migrant workers associated with globalization are a potential source for DENV/CHIKV introduction into nonendemic areas and outbreaks (2-4, 8). These outbreaks are considered to result from the transmission from a single viremic patient into an *Ae. aegypti* or *Ae. albopictus*-infested area. In fact, the first autochthonous outbreak of dengue fever since 1944 occurred in Maui and Oahu from September 2001 to April 2002, which included 122 laboratory-confirmed recent infections from 1,644 persons with locally dengue like illness) (16). Epidemiologic and virologic analysis concluded that *Ae. albopictus* was considered to be an epidemic dengue vector in this outbreak and that travelers brought the virus from French Polynesia, 4,400 km south of Hawaii.

An outbreak with CHIK fever happened in the Italian province of Ravenna, a temperate region, and infected 350 people from July to September 2007 (17). Continual surveillance elucidated that one tourist brought this outbreak from India. He developed a febrile illness 2 days after arrival in Ravenna, and was later confirmed by serology to be recent CHIKV infection. *Ae albopictus* mosquitoes settled in Italy in 1990s, where samples of the mosquitoes from the villages were positive for CHIKV.

Fortunately, the present case happened in January and no other family members developed CHIK fever. However, if cases appear in the summer, careful surveillance will be mandatory in Japan since *Ae albopictus* is distributed widely except for the northernmost regions of Aomori and Hokkaido (18).

Globally, the number of international travelers continues to grow from 457 million in 1990 to 763 million in 2004, and it will reach 1.6 billion by the year 2020 (19). We are facing a potential threat in which the endemic disease can easily cross geographic borders by globalization and transmission to remote areas by airplane. Therefore, a reportable system, including announcements to clinicians concerning epidemiology, and easy access to diagnostic tests for these febrile diseases should be promptly established in Japan. In a CHIK fever outbreak in 2006, several clinicians reported that the Internet surveillance network was helpful in the diagnosis of returning travelers and reduced the risk of the infection in travelers through real-time epidemiology (9). Thus, global collaboration focusing on public education, vector control, surveillance system to detect the early recognition of local transmission, and ultimately, vaccination development are essential in order to eradicate threats of a CHIKV epidemic in nonendemic, as well as in endemic regions.

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References