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**Short Communication**

# Chikungunya Fever in Japan Imported from the Caribbean Islands

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**SUMMARY:** A 53-year-old Japanese woman who was working as a volunteer in the Commonwealth of Dominica in the Caribbean islands presented with a high-grade fever and severe incapacitating generalized arthralgia. The Asian genotype of the chikungunya virus was confirmed using reverse transcription-PCR and serology, based on the presence of a specific neutralization titer and immunoglobulin M antibodies. She was diagnosed with post-chikungunya chronic arthritis based on persistence of her polyarthritis for 3 months and the presence of rheumatoid factor, immunoglobulin G-rheumatoid factor, and matrix metalloproteinase-3. Chikungunya virus should be considered as a causative pathogen in travelers returning from Caribbean islands. Clinicians should consider chikungunya fever in the differential diagnosis of patients who complain of chronic arthritis and have a history of travel to an endemic area.

Chikungunya fever (CHIKF) is a re-emerging infectious disease. The first isolation of the Chikungunya virus (CHIKV) in the Western Hemisphere, in the French West Indies, was reported in December 2013 (1). Since then, CHIKV has been found in other Caribbean islands and has spread to North and South America with just over 1,280,000 suspected cases in the region up until October 2014 (2). The Centers for Disease Control and Prevention and the European Centre for Disease Prevention and Control (ECDC) have reported numerous imported cases of CHIKF from the Caribbean islands to the United States and European countries, respectively (3,4). As globalization continues, CHIKV from the Caribbean islands has also become a threat to Asian countries.

A previously healthy 53-year-old Japanese woman who was working as a volunteer in the Commonwealth of Dominica in the Caribbean islands from early to mid-June 2014 suddenly developed a high-grade fever and severe incapacitating generalized arthralgia. She immediately returned to Japan. On arrival, she was tested at the Narita Airport Quarantine Station for malaria and dengue fever using rapid diagnostic tests, such as that targeting the dengue virus (DENV) NS1 antigen. Both tests yielded negative results. The patient was convalescing from her symptoms at home. CHIKV RNA by reverse transcription-PCR of her serum that had been extracted on the day she returned home (day 5 after returning to Japan) was detected at the quarantine station (5). With this confirmation of CHIKF, she was admitted to our hospital the same day following the instructions of the quarantine station. The sequence of the E1 surface glycoprotein gene of CHIKV derived from the patient's peripheral blood was classified as an Asian genotype, which shares conserved sequences with endemic virus strains in the Caribbean islands.

Physical examination revealed fever and arthritis with swelling in the ankles, knees, elbows, wrists, and finger joints. From day 4 after her return to Japan, a generalized spotted rash developed over her entire body except her face (Fig. 1). Blood tests revealed the presence of leukopenia but no remarkable thrombocytopenia. Laboratory examinations revealed a white blood cell count of $3.5 \times 10^3/\mu L$, hemoglobin level of 13.6 g/dL, platelet count of $17.1 \times 10^4/\mu L$, lactate dehydrogenase level of 254 IU/L, and C-reactive protein level of 0.3 mg/dL. Virological examinations demonstrated the

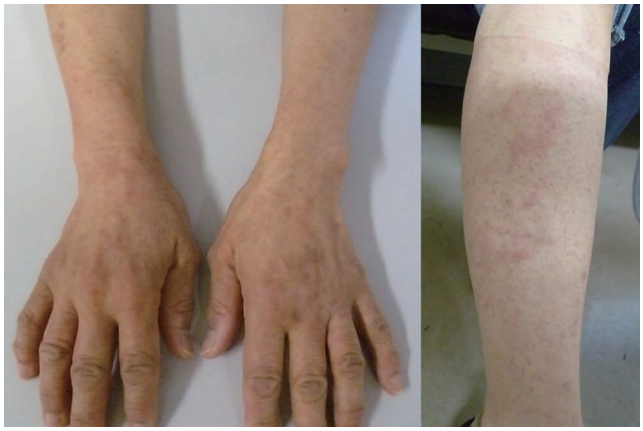

Fig. 1. (Color online) Spotted rash with Chikungunya fever.

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Table 1. Laboratory findings in an imported case of Chikungunya fever in Japan

| Laboratory test | | Day[1] | | | |
|---|---|---|---|---|---|
| | | 3 | 7 | 13 | 47 |
| WBC | $\times 10^9$/L | NT | 3.5 | 5.3 | 5.8 |
| Platelet count | $\times 10^{10}$/L | NT | 17.1 | 22.3 | 25.3 |
| CHIKV-RNA | | (+) | ND | ND | ND |
| CHIKV-neutralization titer[1] | | <10 | 10× | 160× | >320× |
| CHIKV-IgM captured ELISA[2] | P/N ratio | (−) | 1.92 (±) | 3.30 (+) | NT |
| RF | IU/mL | NT | NT | 48[3] | 73[3] |
| IgG-RF | AU/mL | NT | NT | 56.8[3] | 79.1[3] |
| anti-CCP | U/mL | NT | NT | <0.6 | <0.6 |
| MMP-3 | ng/mL | NT | NT | 41.5 | 77.9[3] |

ND, not detected; NT, not tested; RF, rheumatoid factor; IgG-RF, immunoglobulin G-rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibody; MMP-3, matrix metalloproteinase-3.
[1]: Days when the sample was taken from symptom onset. [2]: Neutralization titers were determined by the 90% plaque reduction test. P/N ratio; positive >2.2, negative ≤1.8. [3]: Positive result.

presence of a CHIKV-specific neutralization titer and immunoglobulin M (IgM) antibodies. Although the rash had completely disappeared without residual pigmentation 1 week after her admission, the intolerable arthritis in her ankles, wrists, and finger joints persisted for 3 months. Serum rheumatoid factor (RF) and immunoglobulin G-RF (IgG-RF) were positive, but anti-cyclic citrullinated peptide antibody (anti-CCP) remained negative. Matrix metalloproteinase-3 (MMP-3), which plays a pivotal role in the degradation of cartilage components in rheumatoid arthritis (RA), was within the normal limit at the first examination but became positive 1 month later (Table 1). Because her clinical findings fulfilled the criteria for RA according to the American College of Rheumatology, she was eventually diagnosed with post-chikungunya chronic arthritis (PCCA).

At present, cases of local vectorial transmission of CHIKF in previously non-endemic regions are thought to be caused by imported CHIKV from the Caribbean islands; such cases are on the rise in South and Central American countries and in the Pacific Islands. A literature search revealed that the present case is the first imported case of CHIKF from the Caribbean islands not just in Japan but also in Asia and Oceania. Imported cases of CHIKF in travelers returning from the same region have been identified in Asia (15 cases) and Oceania (12 cases) (2). In these circumstances, merely treating the patient is obviously not adequate to end a possible outbreak of CHIKF. History tells us that we should act swiftly to prevent local transmission and outbreak of the imported disease.

Quarantine stations in Japan currently examine travelers complaining of fever, and over 50 cases of imported CHIKF have been identified in Japan since 2006. Nine imported cases of CHIKV have been reported in the English literature since 2006, all of which were imported from South and Southeast Asia, namely, Sri Lanka ($n$ = 2), India ($n$ = 1), Indonesia ($n$ = 3), Malaysia ($n$ = 2), and Thailand ($n$ = 1) (5–8). Viremia in CHIKV-infected individuals typically last for 4–6 days after the onset of illness; therefore, the early detection of imported cases is critical to prevent local transmission in non-endemic countries. This case emphasizes the importance of the quarantine surveillance system for febrile travelers returning from CHIKV-endemic countries. However, as the incubation period is considered to be 1–12 days, the current quarantine system is technically unable to identify CHIKV-infected asymptomatic travelers returning from CHIKV-endemic countries and can possibly overlook these cases of CHIKV in Japan. The main vectors that transmit CHIKV are the same *Aedes* mosquitoes—*Aedes aegypti* and *Aedes albopictus*—that are the vectors for DENV. In particular, *Ae. albopictus* has played an important role in CHIKV transmission in recent outbreaks, including that in La Reunion Island in the Indian Ocean (9). This widely invasive species is well known in many European countries, and the ECDC has already alerted the authorities to the risk of local vectorial transmission of imported CHIKV (10). Indeed, a 2007 outbreak in Italy demonstrated that imported CHIKV can be transmitted by *Ae. albopictus*, which is indigenous in Japan (except in Hokkaido and Aomori Prefecture) (11). The potential risk for local vectorial transmission of CHIKV is a real one, particularly considering the recent local outbreak of DENV in Japan (August to October, 2014) (12), which demonstrates the transmission capacity of indigenous mosquitoes in causing infections among residents who did not travel to DENV-endemic countries.

Although CHIKV infection was previously described as a self-limiting infectious disease, severe arthralgia persists in more than 60% of patients (13). Chronic rheumatoid-like polyarthritis known as PCCA that sometimes leads to destructive arthropathy occurs in around 5.6% of patients after acute CHIKV infection (14). PCCA was previously reported after an East/Central/South African (ECSA) genotype infection, but a case of PCCA caused by the Asian genotype, as well as our case, was also reported in Saint Martin in the Caribbean islands in 2013 (15). Therefore, it is important to consider that the epidemic Asian genotypes could be a causative pathogen for PCCA. Based on the observation of the outbreak of the ECSA genotype in La Reunion Islands in 2005 to 2006, RF and anti-CCP antibodies could be detected in 12.5–57.1% and 28.6–56.5% of patients with PCCA, respectively (14,16,17). In our case, not only RF but also IgG-RF could be detected in the early chronic phase, within 2 weeks of the onset of clinical symptoms. Additionally, we confirmed the elevation of MMP-3, which is a specific marker related to the activity of RA. We should consider CHIKF when a patient with a history of travel to CHIKV-endemic areas, including the Caribbean islands, complains of generalized arthritis accompanied by elevation of these markers.

As the number of international travelers increase with globalization, imported CHIKV cases could increase in non-endemic countries. Moreover, the emerging cases of DENV in Japan indicate the need for all possible preventive measures against CHIKV spreading domestically. Travelers who visit endemic regions should be alerted to the risk of CHIKF and advised to protect themselves against mosquito bites. In addition, early

detection and management of infected patients would obviously reduce the risk of local transmission caused by imported CHIKV. Not only the ECSA genotype but also the Asian genotype causes PCCA associated with autoantibodies in RA. CHIKV infection should be considered in patients who have rheumatoid-like symptoms returning from CHIKV-endemic countries including those in the Western Hemisphere.

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**Conflict of interest** None to declare.

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