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Brief communication

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# Zika fever imported from Thailand to Japan, and diagnosed by PCR in the urine

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## Abstract

In July 2014, a Japanese traveller returning from Thailand was investigated for fever, headache, rash and conjunctivitis. Zika virus RNA was detected in his urine sample by real-time reverse transcription polymerase chain reaction. Serological tests showed cross reactivity of IgM against the dengue virus. Zika fever could be misdiagnosed or missed and should be considered in febrile patients with a rash, especially those returning from Thailand.

**Key words**: Zika fever, Mosquito-borne disease, Flaviviridae

Zika fever is a mosquito-borne viral illness caused by caused by Zika virus (ZIKV). The clinical course of Zika fever is similar to that of Dengue fever, which is characterized by fever, joint pain, myalgia, headache and rash. The cross reactivity with the antibody against other flavivirus may lead to misdiagnosis, and detection of ZIKV in blood or urine using polymerase chain reaction (PCR) is highly specific. We report an imported Zika fever case from Thailand to Japan, diagnosed by detection of ZIKV in urine using PCR.

## Case Description

A previously healthy man in his early 40s presented to the National Center for Global Health and Medicine, in Tokyo, Japan, on 4th August with a 3-day history of fever, headache and rash after returning from Thailand. He was sightseeing in Koh Samui, an island in Thailand, from 25 to 31 July 2014. He did not use an insect repellent during this period. Fever (self-reported) with headache developed on 2nd August, followed by diffuse maculopapular rash on his trunk and extremities.

At the initial presentation, his body temperature was 37.2°C; physical examination revealed bilateral non-purulent conjunctivitis, diffuse maculopapular rash on the face, trunk (Figure 1), extremities, including his palms and soles (Figure 2). Other examinations yielded normal results. Laboratory examination revealed a slightly elevated C-reactive protein level of 1.12 mg/dl (reference value < 0.3 mg/dl), normal white blood cell count of 4940/$\mu$l and normal platelet count of 184 000/$\mu$l. An examination with the rapid diagnosis kit for the dengue virus (DENV, Dengue Duo NS1 Ag + Ab Combo; SD BIOLINE, Standard Diagnostics Inc., Korea) showed negative results for NS-1 antigen and IgM and IgG antibodies (Abs) for DENV.

We suspected Zika fever clinically, and sent his blood sample to the National Institute for Infectious Diseases (NIID) in Japan.

At the second visit, 3 days after the initial presentation, his fever and headache had resolved but the rash and conjunctivitis remained. At the third consultation, 11 days after the initial presentation, all of his signs and symptoms had resolved.

ZIKV RNA was detected in his urine sample collected 7 days after symptom onset by the real-time reverse transcription PCR RT-PCR) performed at the NIID, as opposed to the equivocal findings yielded by the examination of the serum samples taken at the first presentation (2 days after symptom onset).

**Figure 1**. Maculopapular rash on the trunk in a case of imported ZIKV infection from Thailand, Japan, July 2014

**Figure 2**. Maculopapular rash on the hand in a case of imported ZIKV infection from Thailand, Japan, July 2014

Follow-up serum samples were collected on 7 and 13 August 2014, 5 and 11 days after symptom onset, respectively. The second and third serum samples showed a significant increase in the anti-ZIKV-IgM index, anti-DENV IgM Abs index, anti-DENV IgG Abs index and negative results for the DENV non-structural Protein 1 antigen. The increase in the anti-ZIKV IgM Abs index was significantly higher than the increase in the anti-dengue IgM Abs index (Table 1).

## Discussion

ZIKV was first isolated in 1947 from the rhesus macaque living in the Zika forest in Uganda.[1] ZIKV belongs to the family *Flaviviridae* and genus *Flavivirus*, which also includes the DENV, West Nile virus and yellow fever virus. Cases of Zika fever in humans were reported in African countries (Uganda, Tanzania, Central Africa, Sierra Leone and Egypt) and Asian Countries; Thailand, India, Malaysia, the Philippines, Vietnam and Indonesia. In recent years, outbreaks of Zika fever have been reported in the Yap Island in Micronesia[2] and French Polynesia.[3] In Japan, two cases of Zika fever imported from French Polynesia were reported in 2014. Zika fever was diagnosed in one traveller each who had returned from Thailand to Germany and Canada, respectively.[4,5] The German traveller had visited Phuket, Krabi, Koh Jum and Koh Lanta, and the Canadian traveller, Phuket and Bangkok. So far, nine cases of imported Zika fever have been reported. We have summarized all imported cases in Table 2.

The most commonly reported symptoms of Zika fever are fever, rash, fatigue, arthritis or arthralgia and conjunctivitis.[10] There are limited laboratory data about Zika fever, but some previous cases did not show thrombocytopenia,[5,9] similar to that in our patient, who neither showed leucopenia. The clinical course of Zika fever is mild and self-limiting but one case of a patient presenting with Guillain–Barre syndrome after acute infection was reported.[11] Diagnosis is made by serology, detection of IgM or neutralizing Abs against ZIKV or by detection of ZIKV RNA using PCR. Cross reactivity with IgM against other flaviviruses, such as the dengue or yellow fever virus was previously reported, as seen in our case.[12]

In this case, ZIKV was detected by urine examination by real-time RT-PCR and not serum examination. This phenomenon was also seen in one of our previously reported cases.[3] Gourinat *et al.*[13] have recently reported the usefulness of urine samples for detecting ZIKV. They reported that urine samples were positive even over 10 days after onset of the disease. From these findings, ZIKV persists longer in urine than in blood, urine samples will be better than serum samples for detecting ZIKV in the recovery phase.

## Conclusion

To best of our knowledge, this is the first report of Zika fever case that was infected in Koh Samui, Thailand. Our case was diagnosed by detecting ZIKV in urine sample using PCR. The similar clinical features and the limited cross reactivity of IgM against other flaviviruses, especially DENV can lead to misdiagnosis. Travellers can

**Table 1**. Serological test results and virological data of a case of ZIKV infection imported from Thailand into Japan

| Antibody or antigen tested | Number of days after symptom onset at serum sample collection (days) | | |
|---|---|---|---|
| | 2 | 5 | 11 |
| Anti-ZIKV-IgM | Negative (1.77) | Positive (11.4) | Positive (10.9) |
| Anti-DENV-IgG | 1.06 | Positive (1.47) | Positive (1.86) |
| Anti-DENV-IgM | Negative (0.39) | Positive (1.23) | Positive (1.68) |
| DENV NS1 | Negative (0.33) | Negative (0.28) | Negative (0.28) |

**Table 2**. Literature review of imported cases of Zika fever

| Author | Reported year | Age | Sex | Country of residence | Country of likely acquisition | Reference |
|---|---|---|---|---|---|---|
| Zammarchi L *et al*. | 2015 | Early-60s | M | Italy | Salvador de Bahia, Brazil | (6) |
| Tappe D *et al*. | 2015 | 45 | F | Germany | Borneo, Malaysia | (5) |
| Zammarchi L *et al*. | 2015 | Early-30a | M | Italy | French Polynesia | (7) |
| Zammarchi L *et al*. | 2015 | Early-30s | F | Italy | French Polynesia | (7) |
| Fonseca K *et al*. | 2014 | NA | F | Canada | Phuket, Thailand | (4) |
| Tappe D *et al*. | 2014 | 50s | M | Germany | Phuket, Krabi, Ko Jum, Ko Lanta, Thailanda | (5) |
| Kutsuna S *et al*. | 2014 | Mid-20s | M | Japan | French Polynesia | (3) |
| Kutsuna S *et al*. | 2014 | Early-30s | M | Japan | French Polynesia | (3) |
| Wæhre T *et al*. | 2014 | 31 | F | Norway | Tahiti | (8) |
| Kwong JC *et al*. | 2013 | 52 | F | Australia | Jakarta, Indonesia | (9) |
| This case | | 40s | M | Japan | Ko Samui, Thailand | |

NA, not available.

be infected with the ZIKV during short trips; a case of Zika fever in an Australian traveller returning from a short trip to Indonesia was previously reported.[12] Given these facts, clinicians should suspect Zika fever when we examining patients returning from the Southeast Asia with dengue-like symptoms and unusual serological tests results, especially negative results for non-structural Protein 1 antigen on real-time RT-PCR.

**Conflict of interest:** None declared.

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