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CASE REPORT

Clinical and radiological features of imported chikungunya fever in Japan: a study of six cases at the National Center for Global Health and Medicine

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Abstract Chikungunya fever (CHIKF) is currently distributed in Africa and in South and Southeast Asia; outbreaks have occurred periodically in the region over the past 50 years. After a large outbreak had occurred in countries in the western Indian Ocean region in 2005, several countries reported cases of CHIKF from travelers who had visited affected areas. In Japan, there have been only 15 cases of CHIKF patients so far, according to the National Institute of Infectious Diseases. Therefore, to evaluate the clinical and radiological features associated with the disease, we describe 6 imported cases of CHIKF. All of the patients had had prolonged arthralgia on admission to our hospital, and diagnosis was confirmed with specific antibodies by using an IgM-capture enzyme-linked immunoassay and a plaque reduction neutralizing antibody assay. Magnetic resonance imaging (MRI) of one patient revealed erosive arthritis and tenosynovitis during the convalescence stage. Clinicians should be aware of the late consequences of infection by the chikungunya virus (CHIKV) and recognize the possible association of subacute and chronic arthritis features. In addition, competent vectors of CHIKV, *Aedes aegypti,* can now be found in many temperate areas of the eastern and western hemispheres, including Japan. This fact raises concern that the virus could be introduced and become established in these areas. This necessitates an increased awareness of the disease, because imported cases are likely to contribute to the spread of CHIKV infection wherever the competent mosquito vectors are distributed.

Keywords Chikungunya fever · Arthritis · Tenosynovitis · MRI · Synovial fluid

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Introduction

Chikungunya fever (CHIKF) is a viral disease transmitted to humans by the bite of infected mosquitoes. The word chikungunya, which means "to walk bent over" in the Makonde language of Africa, refers to the effect of the disease's incapacitating arthralgia [1]. The chikungunya virus (CHIKV) is an arthropod-borne RNA virus of the genus Alphavirus (Togaviridae family) [2]. Like the dengue virus (DENV), it is transmitted to humans by the *Aedes aegypti* and *Aedes albopictus* species. The clinical symptoms of CHIKF are also similar to those of dengue fever (DF), although hemorrhagic manifestations are relatively rare with CHIKF [3]. CHIKV was first described in 1955 following an outbreak on the Makonde plateau along the border between Tanzania and Mozambique in 1952 [4, 5]. CHIKV is currently distributed in Africa and in South and Southeast Asia, and outbreaks of CHIKF have occurred periodically in these regions for the past 50 years. However, in 2005, a large outbreak occurred in countries in the western Indian Ocean region: Comoros, Mayotte, Mauritius, the Seychelles, and Reunion Island.

Since that epidemic, several countries have reported cases of CHIKF from travelers who had visited affected countries [6]. According to the National Institute of Infectious Diseases in Japan, the number of imported CHIKF patients has been only 17 since the first case was confirmed in 2006 and reported in 2007 [7]; therefore, little clinical information is available in Japan because surveillance reports are not compulsory according to the infectious disease control laws of Japan. In the present study we describe the clinical and radiological features of 6 imported cases of CHIKF in patients who were examined at the Travel Clinic of the National Center for Global Health and Medicine (NCGM).

Case reports

Case 1

The patient was a 36-year-old Japanese woman who had accompanied her husband to Colombo, Sri Lanka, from 16 July to 10 December 2006 [7]. On 17 November she suffered from arthralgia affecting the left leg, with a fever of 40° and headache. The patient was diagnosed with dengue fever (DF) and CHIKF based on the clinical information, leucopenia, thrombocytopenia, and a rapid diagnostic test undertaken at the local hospital. The fever subsided the next day, and a generalized rash developed on the extremities. However, the arthralgia persisted and in spite of anti-inflammatory medication the patient presented to the NCGM with a 40 day history of arthralgia on 26 December 2006.

Case 2

The patient was a 52-year-old Japanese man who had stayed in Sumatra, Indonesia, from 26 March to 5 April 2009 to collect butterflies. On 31 March, the patient suffered from arthralgia affecting the wrists, ankles, and knees, and he had a fever of 39.5°. Although the patient was afebrile the following day, the arthralgia persisted. The patient presented to the NCGM with a 59 day history of arthralgia on 28 May 2009.

Case 3

The patient was a 30-year-old Japanese man who had visited Java, Indonesia, from 26 March to 5 April 2009 for a public performance. On 13 May the patient suffered from fever, headache, arthralgia, and a skin rash. The arthralgia persisted even though the fever had subsided by 17 May, and the patient presented to the NCGM with a 41 day history of arthralgia on 22 June 2009.

Case 4

The patient was a 39-year-old Japanese woman who had accompanied her husband to Kuala Lumpur, Malaysia, from 4 April to 28 June 2009. On 12 May the patient suffered from a fever of 39.5°, arthralgia, a skin rash, and gingivitis. The patient was examined and a screening test for collagen diseases was undertaken at the local hospital. Despite normal results from all examinations, the arthralgia persisted, and the patient presented to the NCGM with a 50 day history of arthralgia on 30 June 2009.

Case 5

The patient was a 56-year-old Japanese woman who had visited Phuket and Bangkok, Thailand, from 3 to 7 September 2009 for leisure. On 8 September, the patient suffered from arthralgia, followed by back pain and a fever of 38.5° the next day. The patient was examined twice, with a rapid diagnostic test for influenza and a screening test for collagen diseases at another hospital. On 11 September, a generalized spotted rash developed on both extremities and lasted for 4 days, and the patient presented to the NCGM on 14 September 2009.

Case 6

The patient was a 39-year-old Japanese woman who had visited Sumba and Bali, Indonesia; Ho Chi Minh City, Vietnam; Siem Reap and Phnom Penh, Cambodia; and Bangkok and Ayutthaya, Thailand, from 13 February to 25 April 2009 for leisure. On 26 February, the patient suffered from fever, headache, myalgia, and arthralgia. On 3 March, a generalized spotted rash developed on both arms and lasted for 4 days. The patient was examined at a local hospital in Jakarta on 6 March. The patient suffered from fever with a cough and sore throat from 26 April, possibly due to influenza A. The patient presented to the NCGM with a 62-day history of arthralgia on 28 April 2009.

All patients except for Case 5 had had prolonged arthralgia on admission. The clinical and laboratory data of all patients is shown in Tables 1 and 2. The diagnosis was confirmed with specific antibodies by an IgM-capture enzyme-linked immunoassay and a plaque reduction neutralizing antibody assay (PRNT). It was not possible to detect the CHIKV genome by real time polymerase chain reaction (PCR) (TaqMan, Foster City, CA, USA) [8] in any of the patients. But in Case 5, IgM and neutralizing antibodies were detected (1: 20) in synovial fluid for 3 months.

Magnetic resonance imaging (MRI) was performed in Cases 2 and 5 (the other patients did not consent to the performance of MRI), with the imaging in Case 2 revealing erosive changes and possible mild tenosynovitis with

Table 1 Detailed clinical information of each case

	Age (years)/sex	Underlying disease	Place of contraction (city)	Duration of stay	Symptom at onset (site of arthralgia)	Duration of fever (days)	Skin rash	Joint swelling	Symptom and symptom duration on admission	Duration of arthralgia
Case 1	36/female	None	Sri Lanka (Colombo)	5 months	Fever, headache, arthralgia (ankle)	1	Present	Absent	5 weeks arthralgia	5 months
Case 2	52/male	Hypertension	Indonesia (Sumatra)[a]	2 weeks	Fever, arthralgia (wrists, ankles, knees)	1	Absent	Absent	6 weeks arthralgia	4 months
Case 3	30/male	None	Indonesia (Java)[a]	2 months	Fever, arthralgia (ankle, knee, shoulder)	4	Present	Absent	5 weeks arthralgia	Unknown
Case 4	39/female	None	Malaysia (Kuala Lumpur)	2 months	Fever, skin rash, arthralgia (shoulders, wrists, ankles)	4	Present	Absent	5 weeks arthralgia	3 months
Case 5	56/female	None	Thailand (Phuket)	5 days	Fever, backpain, arthralgia (finger, elbow, shoulder)	2	Present	Present	3 days arthralgia joint swelling	8 months
Case 6	39/female	None	Indonesia (Sumba)[a]	3 weeks	Fever, headache, myalgia (fingers, shoulder, back)	3	Present	Absent	9 weeks arthralgia (Fever, cough)[b]	Unknown

[a] Island in Indonesia

[b] These symptoms were possibly due to influenza

effusions in the wrist and hand at 2 months after the occurrence of the initial symptoms (Fig. 1a). Imaging in Case 5 revealed a small fluid collection in the wrist 6 months after the initial symptoms, in spite of the lack of specific findings on admission (Fig. 1b).

The arthralgia in all the patients resolved after several months of treatment with or without nonsteroidal anti-inflammatory drugs. All of our presented cases failed to fulfill the criteria for rheumatoid arthritis (RA) according to the American College of Rheumatology (ACR).

Discussion

The chief complaint in the patients whose cases are presented here was persistent arthralgia for more than two months, except in Case 5. Although fever and polyarthralgia are the two chief clinical features of CHIKF, polyarthralgia is particularly important for the differential diagnosis of CHIKF and dengue fever (DF) [9].

Chronic arthritis following CHIKF has been well documented [10] and it has also been documented as mimicking RA [11]. Therefore, there is a difficulty in differentiating between the onset of RA and persistent arthritis secondary to CHIKF [12]. In an Indian study, around 36% of the CHIKF patients in the cohort met the ACR criteria to classify a patient as having RA [13]. Among travelers returning from the tropics, febrile exanthema with arthralgia is not specific to CHIKF and may be observed with other viral and bacterial infections, particularly DF. On the other hand, severe bilateral and symmetrical arthritis which mimics RA can be seen in most patients after the febrile stage of CHIKF [14]. It is clear that CHIKF patients could easily require referral for rheumatologic evaluation long after their acute febrile illness, when only an alert clinician taking into account the patient's travel history to endemic areas might make the correct diagnosis. Therefore, CHIKF should be suspected in patients with RA-like features who have a history of travel to endemic areas. Clinicians should be aware of the late consequences of infection by CHIKV and recognize the possible association of subacute and chronic arthritis features. If there are suspected cases, the virus should then be confirmed by serological testing.

Following the change from the acute phase to the chronic phase of arthritis, more than half of patients infected by CHIKV have severe tenosynovitis, commonly involving the wrist and fingers, and this may persist for several months to years [15]. In our study, Case 2 revealed erosive arthritis and tenosynovitis, and in Case 5, MRI revealed the collection of a small amount of fluid in the wrist. Although MRI findings of chronic arthritis following CHIKV infection have been documented [13], the MR

Table 2 Laboratory data of each case

	WBC (μl^{-1})	PLT ($\times 10^4/\mu l$)	GOT (IU/l)	GPT (IU/l)	CRP (mg/dl)	RF	PCR	IgM	NT (on admission)
Case 1	9940	29.2	16	13	0.24	NA	(−)	(+)	640
Case 2	5190	16.7	25	28	0.03	(−)	(−)	(+)	320
Case 3	5190	22.9	17	19	0.03	(−)	(−)	(+)	320
Case 4	4170	18.6	16	10	0	(−)	(−)	(+)	20
Case 5	4020	18.7	23	15	0.28	(−)	(−)	(+)[a]	20[a]
Case 6	6300	27.9	38	47	1.6	(+)	(−)	(+)	40

NT was regarded as positive if the titer was more than 10

PLT platelets, *CRP* C-reactive protein, *RF* rheumatoid factor, *PCR* polymerase chain reaction, *NT* neutralization test, *NA* not available

[a] IgM and neutralizing antibodies were detected not only in serum but also in synovial fluid

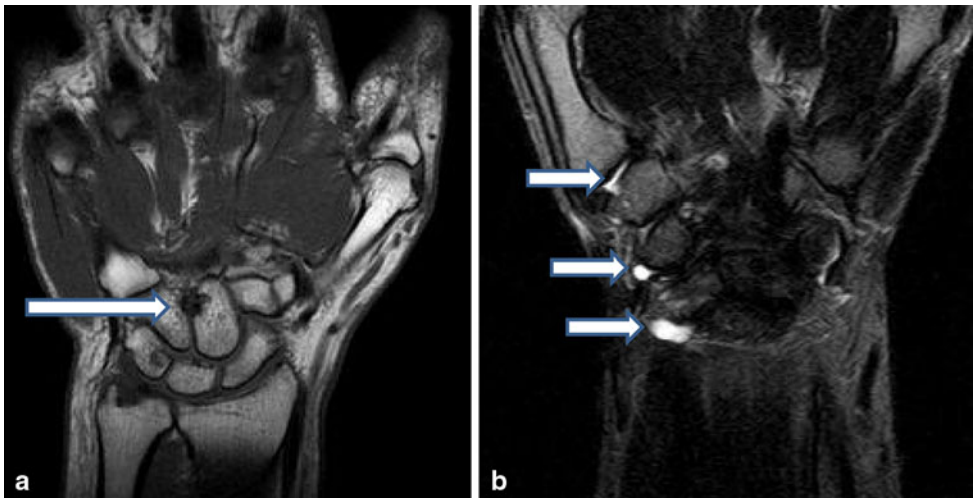

Fig. 1 Coronal magnetic resonance (MR) T1 image in Case 2 (**a**) reveals extensive intermediate-signal-causing carpal styloid erosions (*arrow*), similar to those of rheumatoid arthritis. Axial MR T2 image (**b**) reveals small fluid collections in the wrist (*arrows*) in Case 5

imagings in our Cases 2 and 5 were very clear and similar to those of patients with early-stage RA. Although not all cases of CHIKV infection show erosive arthritis on MRI, this imaging technique could be a valuable diagnostic tool to assist in the management of persistent arthritis in CHIKF patients. In addition, it is very interesting that CHIKV titers were detected in synovial fluid in one of our patients (Case 5). This finding indicates that CHIKV may be present in the synovial fluid in the acute phase, and it is possibly involved with the prolonged arthralgia seen in CHKF patients.

From the viewpoint of disease surveillance, *Aedes albopictus,* which is one of a number of competent CHIKV vectors, can now be found in many temperate areas of the eastern and western hemispheres, including Japan [16]. This fact raises concerns that the virus could be introduced and become established in these areas [17]. In fact, an outbreak of CHIKF occurred in the Italian province of Ravenna, and 350 people were infected from July to September in 2007; this is the first documented local vector-borne transmission of CHIKV in a country with a temperate climate [18]. Such findings necessitate an increased awareness of the disease, because imported cases are likely to contribute to the spread of CHIKV infection wherever the competent mosquito vectors are distributed.

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