

Polyarthritis in four patients with chikungunya arthritis

Nai Lee Lui¹, MRCP, MMed, Hoe Nam Leong², MRCP, MMed, Julian Thumboo^{1,3}, MMed, FRCPE

ABSTRACT The incidence of chikungunya infection in Singapore has been on the rise since the first reported case in 2006. Acute polyarthritis, a common manifestation among affected patients, may precede fever and present with debilitating arthritis to rheumatologists, orthopaedists, internists and primary care physicians. The diagnosis of chikungunya infection requires careful history taking and a high index of suspicion, with supporting evidence from the reverse transcription-polymerase chain reaction or the chikungunya IgM serology test. Treatment of chikungunya arthritis usually involves non-steroidal anti-inflammatory drugs. Rarely, polyarthritis in chikungunya may persist even after resolution of the acute infection, necessitating treatment with disease-modifying anti-rheumatic drugs. In this article, we present the different manifestations of chikungunya arthritis in our local setting and review the literature.

Keywords: arthritis, chikungunya
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INTRODUCTION

Chikungunya virus is an arbovirus belonging to the genus *Alphavirus* (*Togaviridae* family). It is a tropical disease and is geographically distributed from Africa through Southeast Asia and South America. Transmission to humans is mainly via the *Aedes* mosquitoes. Since the first documented epidemic in Tanzania in 1953, chikungunya has caused numerous outbreaks in Africa and Southeast Asia.⁽¹⁾ There are now increasing reports of chikungunya infection in countries outside endemic areas, usually the result of returning travellers from affected countries.⁽²⁾ With globalisation, the disease may gain a foothold in countries with competent vectors. The threat in Singapore is high with its resident *Aedes aegypti* and *Aedes anopheles* mosquitoes.

The first reported case of chikungunya infection in Singapore occurred in late 2006. There were three cases in 2006 and ten in 2007, all of which were imported.⁽³⁾ The first local outbreak in 2008 occurred between January 14, 2008 and February 21, 2008, during which time a total of 13 patients were confirmed to have chikungunya infection.⁽⁴⁾ Subsequently, government census data showed that there were 690 and 351 cases reported in 2008 and 2009, respectively, suggesting local transmission and endemicity.⁽³⁾

Individuals with chikungunya infection present with high fever, headache, back pain, myalgia and arthralgia. The latter can be intense, affecting the extremities (ankles, wrists and phalanges) and large joints. The pattern of arthralgia/arthritis tends to be erratic and may relapse after a period of recovery. Pain may be intense and incapacitating, and may persist for several months.⁽¹⁾ Diagnosis is dependent on a coherent history, with an appropriate laboratory test – a rising serological IgM titre or positive reverse transcription-polymerase chain reaction (RT-PCR).

Infection remains the most common aetiology for patients with fever and acute polyarthritis. In Singapore, the differential diagnosis must now include chikungunya infection even in the absence of recent travel. Individuals afflicted with chikungunya

may present with arthralgia or arthritis. Detailed history and careful physical examination, with a high index of suspicion, are essential for the accurate diagnosis of this emerging infection. The following four cases highlight the different patterns that chikungunya arthritis may present with (Table I).

CASE 1

A 69-year-old woman with a history of breast cancer (in remission since 1994) was admitted in January 2009 with a four-day history of severe polyarthralgia. She had low-grade fever and pharyngitis for ten days prior to the development of arthralgia. There was concomitant diarrhoea in the first few days of illness, which had stopped prior to admission. The patient remained afebrile throughout her inpatient stay. Synovitis was noted over both elbows, the left wrist, multiple proximal interphalangeal joints (PIPs), both ankles and the metatarsophalangeal joints (MTPJs).

Given the acute nature of arthritis, the patient was diagnosed with virus-related arthritis, but was also investigated for possible bacteria-related reactive arthritis in view of recent diarrhoea and pharyngitis. Stool cultures were negative for *Salmonella* spp., *Vibrio* spp., *Yersinia* spp. and *Campylobacter* spp., and the serum anti-streptolysin O titre was not elevated. Arthralgia persisted despite treatment with non-steroidal anti-inflammatory drugs (NSAIDs). Relevant tests demonstrated a weakly positive rheumatoid factor (RF; 13.7 u/mL) and the absence of anti-cyclic citrullinated peptide (CCP) antibodies. Antinuclear antibody was also absent. Significantly, chikungunya RT-PCR was positive. Dengue IgM was found to be positive, but apart from the fever, co-infection was deemed unlikely, as there were no other signs or symptoms of dengue or any haematological abnormalities such as haemoconcentration or thrombocytopenia. Antiparvovirus B19 IgM serology was also negative during hospital stay.

Radiographic examination of the patient's hands did not show any evidence of erosions or any features suggestive of

¹Department of Rheumatology and Immunology, ²Department of Infectious Diseases, Singapore General Hospital, Singapore, ³Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Correspondence: Dr Lui Nai Lee, Associate Consultant, Department of Rheumatology and Immunology, Singapore General Hospital, Outram Road, Singapore 169608. lui.nai.lee@sgh.com.sg

chronic inflammatory polyarthritis. She was subsequently treated with cyclooxygenase II inhibitor with gradual improvement in symptoms. The arthralgia was found to have completely resolved on outpatient review one month after discharge.

CASE 2

A 61-year-old man presented with polyarthralgia of three days prior to the onset of fever affecting his shoulders, wrists, knees and PIPJs. Pain was severe with overwhelming stiffness, confining the patient to bed. On admission, the patient appeared flushed and was febrile (temperature 38°C), with synovitis of the shoulders, wrists, knees and the metacarpophalangeal joints and PIPJs. In view of the fever and acute nature of symptoms, the patient was diagnosed with possible reactive arthritis. As he worked in a fish farm with abundant mosquitoes, arbovirus infection was deemed a leading concern. Investigations showed positive chikungunya RT-PCR and chikungunya IgM consistent with chikungunya infection. Both dengue IgM and RF were negative. The patient was treated with anti-inflammatory drugs with good response, and arthritis resolved after one week.

CASE 3

A 60-year-old febrile Chinese woman was admitted in August 2008 with a one-day history of fever (temperature 38°C) and polyarthralgia involving mainly the knees and ankles. The patient had tender and mildly swollen bilateral knee and ankle joints. There was no synovitis or rashes. She was admitted with a probable diagnosis of gout. However, the patient volunteered a history that she was recently under the Ministry of Health's surveillance for chikungunya, as one of her colleagues had the infection. Upon investigations, serum chikungunya RT-PCR was positive but RF was found to be negative. The patient was treated symptomatically and the symptoms resolved three days later.

CASE 4

A 69-year-old man presented with a three-month history of polyarthralgia following chikungunya infection. A resident of Sungai Tiram in Johore Bahru, Malaysia, the patient had initially evaded the chikungunya infection that affected his entire family, but developed fever followed by polyarthralgia several weeks later. The polyarthralgia persisted for three months and did not improve with analgesia. Synovitis was noted over multiple joints – the right shoulder, both wrists, PIPJs, both knees and MTPJs. Upon investigation, the patient was found to have positive serum chikungunya IgM, consistent with a recent infection. Serum RF and anti-CCP antibody were negative. He was treated with an NSAID, but follow-up at six weeks showed that the drug was ineffective in the treatment of his arthritis. A short-term trial dose of prednisolone was therefore introduced. However, the patient defaulted follow-up and the outcome of arthritis is unknown.

DISCUSSION

Mosquito-borne ribonucleic acid viruses causing epidemics of

Table 1. Summary of four patients with chikungunya arthritis.

Finding	Case 1	Case 2	Case 3	Case 4
Age (yrs)	69	61	60	69
Gender	Female	Male	Female	Male
Duration of fever prior to arthralgia (days)	10	-3*	1	A few days
Chikungunya RT-PCR	+	+	+	NA
Chikungunya IgM	-	+	NA	+
Treatment	NSAID, COX-II inhibitor	NSAID	NSAID	NSAID, prednisolone

*Arthralgia preceded fever.

RT-PCR: reverse transcription-polymerase chain reaction; NA: not available; NSAID: non-steroidal anti-inflammatory drug; COX-II: cyclooxygenase II

polyarthralgia/polyarthritis are now a global phenomenon.⁽⁵⁾ The arthritogenic alphaviruses known to affect humans are the Chikungunya, O'Nyong Nyong and Sindbis viruses from tropical Africa; the Ross River and Barnah Forest viruses from the South Pacific; and the Mayaro virus from South America.⁽⁶⁾ Chikungunya infection usually causes an acute illness in the form of fever with chills, rashes and arthralgia, lasting 10–12 days. The result of this illness is best described by the word 'chikungunya', which in Makonde means 'that which bends up' or the characteristic stoop posture assumed by patients afflicted with the severe muscle and joint pains associated with this illness.⁽⁷⁾ The onset of symptoms occurs 1–12 days after the mosquito bites,⁽⁸⁾ and most patients present with a typical acute stage, with fever and incapacitating polyarthralgia.^(9,10) Atypically, arthralgia may precede fever, as was seen in Case 2.

Arthralgia in chikungunya can mimic rheumatoid arthritis. While most cases of chikungunya arthropathy recover within several weeks, up to 12% retain residual joint symptoms for some time (up to 18 months).⁽¹¹⁾ Simon et al identified three types of late-to-chronic chikungunya-related rheumatic manifestations: (1) finger and toe polyarthritis with morning pain and stiffness; (2) severe subacute tenosynovitis of the wrists, hands and ankles; and (3) exacerbation of mechanical pain in previously injured joints and bones.⁽⁹⁾ Not surprisingly, chikungunya virus has been associated with the development of rheumatoid arthritis.⁽¹²⁾

At present, not much is known about the underlying immunopathophysiological processes by which chikungunya virus causes arthritis. The process was thought to be due to inflammatory mediators such as monocyte chemoattractant protein-1 and interleukin-8 that were secreted by infected macrophages following exposure to viral particles in the synovial tissues.⁽⁸⁾ Inflammation may be severe, with resultant necrosis of the skeletal muscle, as was found in the pathological study of Ross River virus (RRV)-infected mouse models.⁽¹³⁾ Further studies using the chikungunya mouse model by Ziegler et al showed not only similar histopathologic muscle changes to the RRV model but also evidence of dystrophic calcification in the joint cartilage of some

mice.⁽¹⁴⁾ The cause of chronic chikungunya arthritis is less clear and was postulated to be due to the alphaviruses' ability to persist in tissue sanctuaries, driving innate immune response to limit viral replication.^(15,16) High levels of cytokines such as interferon-alpha and interleukin-12 were persistent for months in patients with chronic chikungunya arthritis.⁽¹⁷⁾

Chikungunya viral infection can be determined via viral cultures in Vero cell lines, nucleic acid detection with RT-PCR or by detection of Chikungunya-specific IgM antibody (chikungunya IgM serology testing). In acute illness, high levels of viraemia last typically for 4–6 days, and can last for up to 12 days after the onset of illness.^(18,19) RT-PCR is thus extremely useful in determining chikungunya infection in the first seven days of illness.^(17,20) Chikungunya RNA may be detected before the onset of symptoms and may persist even after resolution of fever. Different nucleic acid amplification assays, including RT-PCR and isothermal amplification, have been developed and published.⁽²¹⁾

A rising chikungunya IgM is routinely used to determine the presence of specific chikungunya infection. Two main methodologies are available – enzyme-linked immunosorbent assays and immunofluorescence. Both assays offer high specificity and sensitivity. However, chikungunya IgM antibodies may remain detectable for 12–18 months after natural infection and could reflect co-incident infection rather than acute infection.^(22,23) False positive results for chikungunya IgM may occur due to nonspecific IgM response, for example, in patients with autoimmune conditions such as systemic lupus erythematosus that is not known due to cross-reactivity or co-infection with dengue.⁽²⁴⁾ Co-infection of chikungunya and dengue has been reported in neighbouring Malaysia,⁽²⁵⁾ but the likelihood of this occurring in Singapore was assessed to be very low based on investigations and analysis of past major chikungunya outbreaks.⁽²⁴⁾ In diagnosing acute chikungunya infection, RT-PCR thus remains the diagnostic assay of choice. In three of the four patients presented in this article, diagnosis was confirmed by the presence of a positive RT-PCR result. In Case 4, the significant epidemiological history with a positive IgM for chikungunya serology supported the diagnosis for the arboviral infection. A repeat titre was not performed for this patient for cost reasons.

There is currently no approved antiviral treatment for chikungunya, although some *in vitro* studies have reported the efficacy of certain drugs. Treatment is limited only to supportive care, fluids, antipyretics and analgesia.⁽²⁶⁾ The mainstay treatment of polyarthritis in chikungunya arthritis is NSAIDs, but studies have shown that in individuals with prolonged symptoms, immunosuppressants (e.g. methotrexate, hydroxychloroquine and chloroquine) may be necessary.^(11,27,28) These may be useful in chronic synovitis, as it is likely to be immune-related,⁽²⁹⁾ compared with acute synovitis, which is likely secondary to viraemia.

Chikungunya infection is now endemic in Singapore and is an important consideration in any individual with polyarthritis. While chikungunya arthritis is usually a self-limiting disease, chronic arthritis may ensue in some patients. A prospective study

of these patients may help elucidate the long-term outcome of chikungunya arthritis and its relation with rheumatoid arthritis.

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