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Correspondence

Chronic inflammatory arthritis with persisting bony erosions in patients following chikungunya infection

Sir,

Chikungunya fever, an arboviral disease caused by chikungunya virus (CHIKV), manifests as an acute illness with fever, skin rash and severe and incapacitating arthralgia[1] that may persist for several months or even years[2].Cytokines and chemokines such as interleukin (IL)-6, IL- 8, monocyte chemoattractant protein (MCP)-1 and macrophage inflammatory protein (MIP)-1 appear to play important roles in the pathogenesis of chronic arthritis in CHIKV infection[3]. The persistence of the specific IgM antibodies for months after the initial infection has been observed in several alpha viral infections, probably due to viral persistence but the underlying mechanism is poorly understood[4]. The present report is an update of our earlier study[5]on evolution of joint lesions and arthritic symptoms in patients who had developed chronic arthritis following CHIKV infection and on the immunological response in these patients.

The original study group cohort consisted of 203 patients with chikungunya fever identified during an outbreak in Dakshina Kannada district of Karnataka State, India, in 2008. The presence of CHIKV infection in these patients was confirmed by the presence of anti-CHIKV IgM antibodies. These patients were followed up for a period of 10 months. Ninety four of these 203 patients continued to have arthritic symptoms at the end of 10 months. A subsample of 20 such patients with unresolved arthritic symptoms was subjected to magnetic resonance imaging (MRI) studies, the results of which were reported earlier[5].

The present study was conducted in April 2011, three years after the onset of chikungunya disease in these patients. MRI was repeated in 14 of the 20 patients who had been subjected to MRI at the end of 10 months. These 14 patients were interviewed for the changes in their arthritic symptoms. Blood samples were collected and tested for anti-CHIKV IgM and IgG antibodies by IgM capture ELISA[6] and NovaLisa™ Chikungunya virus IgG capture ELISA (Nova Tec Immundiagnostica GmbH, Germany) respectively. Detailed history of treatment for their arthritic symptoms could not be obtained for these patients because of non-availability of any medical records. The study was approved by the institutional ethics committee of the Regional Medical Research Centre, Port Blair, Andaman and Nicobar Islands, India, and written informed consent was obtained from patients.

Thirteen of these 14 patients had mono-arthritis and one had oligoarthritis. Arthritic symptoms and signs in one of the 14 patients had completely resolved and in two others, the joint pain had substantially reduced. Four patients reported slight improvement and in the remaining seven, the symptoms persisted without change. None of the patients experienced worsening of symptoms. The mean age of the patients who reported that their symptoms persisted was 58.4 yr whereas that of the patients who showed improvement in symptoms was 49.4 yr. Among the five male patients in the study group, two showed persistence of symptoms while among the nine female patients, five showed persistence of symptoms.

The MRI showed that in one patient, there was complete resolution of the lesions and in four others the lesions were regressing. In two patients the lesions appeared to be progressing with involvement of new joints (Carpal and inter-carpal joints, lower ends of radius and ulna). In the remaining seven patients, the radiological abnormalities remained unaltered. Thus in five of the fourteen patients, the radiological abnormalities regressed and in the remaining nine either persisted or progressed (Table). The mean age of the former group of patients was 48.2 yr and that of the latter was 57.1 yr. Among the five male patients in the study group, three showed persistence or progression

Table. ELISA results and symptoms of the patients after three years post chikungunya virus infection

Patient ID	Age (yr) / sex	IgM ELISA after 3 yr	IgG ELISA after 3 yr	Radiological findings of the patients after 3 yr of post CHIKV infection	Salient MRI features of the patients after 3 yr of post CHIKV infection
Ch 331	39/M	Negative	Negative	Recovered	Normal MRI
Ch 06	53/F	Negative	Positive	Regressed	Tendinitis, bursal effusion.
Ch 103	60/F	Negative	Positive	Persisting	Joint effusion.
Ch 11	54/F	Negative	Negative	Persisting	Bony erosions and marrow oedema, minimal joint effusion.
Ch 102	60/F	Negative	Negative	Regressed	Tendinitis with partial tear, effusion into bursa. Degenerative changes in joint.
Ch 69	70/M	Positive	Negative	Progressed	Erosions and effusion in MP joints. Joint deformity (wrist, MP& IP joints).
Ch 133	60/F	Negative	Negative	Regressed	ACL and meniscus tear. Knee joint effusion, subchondral erosion.
Ch 112	65/F	Positive	Positive	Progressed	Osteoarthritis, effusion, synovial thickening and erosions.
Ch 346	48/F	Negative	Negative	Persisting	ACL and meniscus tear, joint effusion, degenerative changes.
Ch 428	60/M	Negative	Positive	Persisting	Marrow oedema, bony erosion, minimal effusion (MP joints).
Ch 517	45/F	Positive	Positive	Persisting	Subchondral erosions (MP& IP joints).
Ch 175	29/M	Negative	Negative	Regressed	ACL tear, minimal effusion.
Ch 561	60/M	Positive	Positive	Persisting	Bony erosions and effusion.
N 1001	52/F	Positive	Positive	Persisting	Tendinitis/partial thicknesstear, degenerative changes, minimal effusion in ogleno humeral joint.

MP, matacarpophalangeal; IP, interphalangeal; ACL, antero collateral ligament

of radiological abnormalities while among the nine female patients, six showed persistence of progression of lesions.

The patient who showed complete resolution of lesions had focal bony erosions and bursitis in the MRI earlier[5]. Although these lesions have disappeared completely, mild joint pain still persisted. Three of the four patients who showed signs of radiological resolution of lesions had tendinitis, calcification and effusion into joints and bursae earlier. The seven patients with persistent lesions had sub-chondral bony erosions, joint effusion and synovial thickening (Fig. A) earlier. While two of these seven patients reported reduction in the intensity of pain since the last follow up, the remaining five patients reported that their joint pain was persisting without any change. The two patients whose lesions were progressing had bony erosions in metacarpals and effusion in metacarpo-phalangeal joints in earlier MRIs. These lesions progressed and the new lesions including erosions and joint effusion appeared in carpal bones, inter-carpal joints and lower ends of radius and ulna (Fig. B).

Among the nine patients with either persistent or progressing lesions, five were positive of IgM anti-CHIKV antibodies, while none of the five patients whose lesions had regressed completely or partially was positive for IgM antibodies. Seven patients were positive for IgG antibodies.

In seven of these patients with post-CHIKV arthritis who could be followed up at the end of three years,the arthritic symptoms remained unabated. In two of the patients the lesions appeared to have progressed and affected new joints.

This group of patients was tested for rheumatoid factor (RF) and anti- cyclic citrullinated protein (CCP) antibody during the follow up at 10 months and all except one patients were found negative for these[5]. These tests were not repeated during the present follow up.

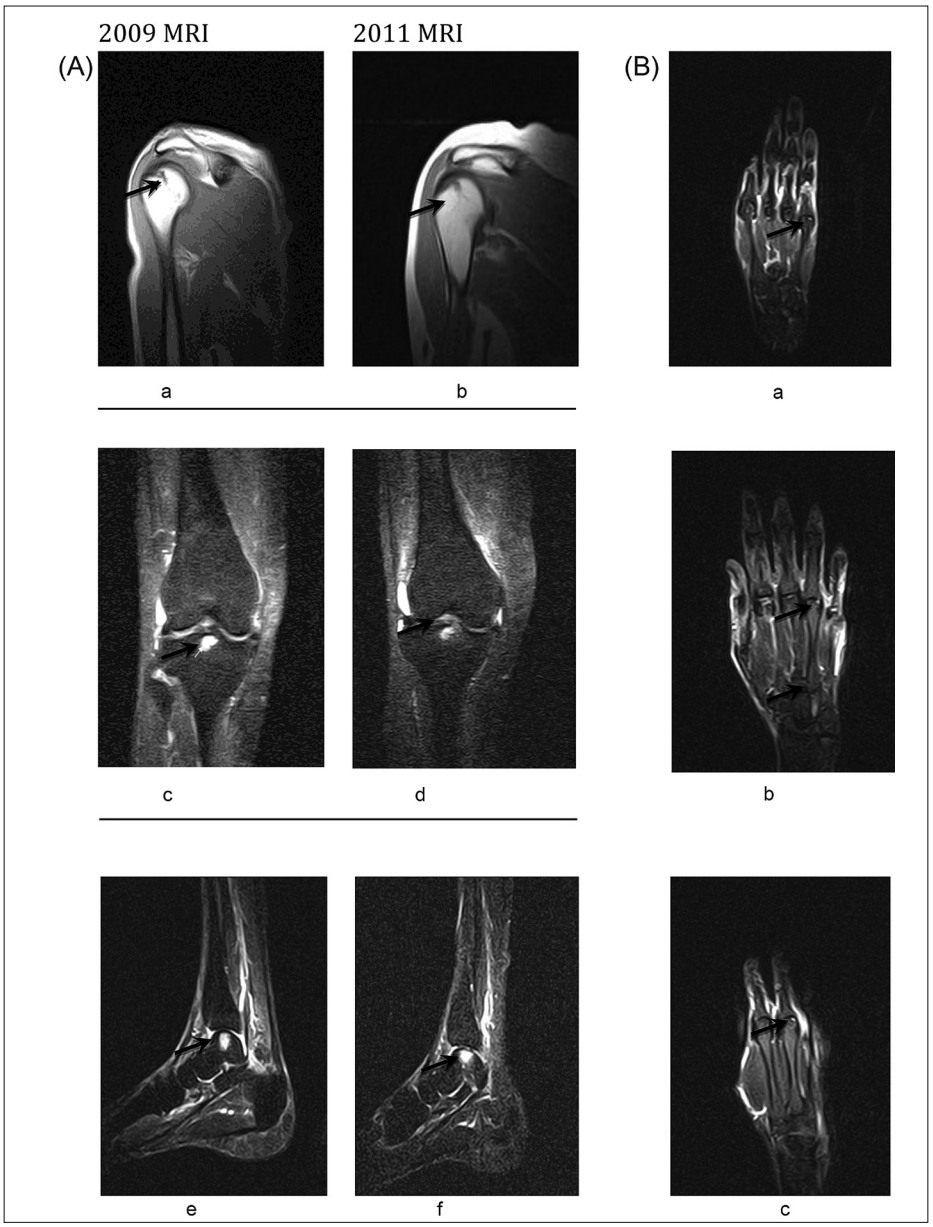

Fig. (A). Persisting Focal Altered signal intensity lesions; (a, b) hypointense on T1 weighed sequence in posterior aspect of head of humerus; (c, d) lesion in intercondylar region of tibia; (e, f) Right Ankle. **Fig. (B).** (a) Lesion in 5th metacarpal with minimal effusion in MP joints of 2nd and 5th fingers at the end of 10th month of post CHIKV infection (2009). Lesions in sub-articular region of head of 3rd, 4th and 5th metacarpal with minimum effusion observed in 3rd to 5th MP joints, new erosion in 3rd and 4th metacarpals. (b, c) at the end of 3 years of post CHIKV infection (2011).

Persistent polyarthralgia and arthritis have been reported in 10 to 20 per cent of patients who suffer CHIKV infection, 20 to 36 months of post infection[2], which mimicked rheumatoid arthritic syndrome. Studies have shown nerosive arthritis and tenosynovitis in patients during the convalescent stage of CHIKV infection[7]. A study on patients with chronic arthritic disability (CAD) after CHIKV infection in Sri Lanka showed that in 6.1 per cent of the patients the debilities persisted at the end of three years of follow up[8].

The present study showed the persistence of detectable IgM against CHIKV after three years post-infection in five of 14 patients with arthritis and in all these patients the joint lesions either persisted or had worsened.

Studies have shown high levels of CHIKV IgM antibodies in Indian patients with post-CHIKV rheumatoid arthritis (RA)-like illnesses[9]. Chronic rheumatism, IgM-anti CHIKV antibodies and elevated IL-6 levels have been shown to persist for a long duration after CHIKV infection[9,10]. Long-term existence of CHIKV in joints, muscles, lymphoid organs, liver and, macrophages in non-human primates has also been documented[11]. Persistence of other alphaviruses such as Ross River virus (RRV) in synovial macrophages has been reported[12] and suggested to be responsible for log-term persistence of IgM antibodies.The present study, although confined to a small number of patients, suggests a possible association of persistent anti-CHIKV IgM antibodies with persistence of arthritic lesions and symptoms.

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