Chikung...What?

By Stephanie Keeling, MD, Msc, FRCPC

Case: The patient was a healthy 46-year-old triathlete, with no past history of arthritis, who went to the Dominican Republic for one week, and returned home with a febrile polyarthritis. Given his history of fever in a returning traveler, his family physician sent off an excellent work-up. In consideration of the differential, this included screens for dengue fever, Chikungunya virus (ChikV; IgM antibody to the Winnipeg Centre for Disease Control [CDC]), Epstein-Barr virus (EBV), malaria, leptospirosis, measles, mumps, rubella, blood cultures for bacterial infections (*e.g.,* meningococcemia), rickettsia, HIV, chlamydia, and gonorrhea. Within one week, during which he received nonsteroidal anti-inflammatory drugs (NSAIDs), his anti-chikungunya IgM came back positive, confirming what was clinically suspected: This patient had textbook ChikV.

When I saw this gentleman in clinic, he was debilitated and miserable. His presentation included significant polyarthritis of his hands, feet, ankles, and knees with superimposed periarticular edema and tenosynovitis. He was negative for any rheumatic serologies, had elevated inflammatory markers, and normal baseline X-rays. Given he had already failed a trial of NSAIDs and was on prednisone (20 mg daily) at first presentation in the rheumatology clinic, we treated him as if he had severe rheumatoid arthritis (RA). Over four months he received combination therapy (25 mg subcutaneous methotrexate weekly with hydroxychloroquine 400 mg daily and sulfasalazine 1 gram twice a day) with partial response only. He failed a recent trial of leflunomide (added to his aforementioned regimen) and is now being assessed for a tumour necrosis factor (TNF)-inhibitor.

While the threat of Zika virus makes nightly news rounds, a related arthropod-borne virus, Chikungunya, should figure into the rheumatologist's mind. First described during an outbreak in Tanzania in 1952, the single-stranded RNA-α virus (belonging to the family *Togaviridae*) has spread to nearly 40 countries in Asia, Africa, Europe (specifically Italy), and most recently, the Americas. The widespread disease is no longer a simple "tropical disease," largely because of the geographic range of the two main mosquito vectors (*Aedes aetypti* and *Aedes albopticus*).

The initial cases in the Americas were reported in December 2013 in the Caribbean island of St. Martin, with eventual local transmission reported in the continental United States in Florida in mid-July 2014. While *Ae. aegypti* is found in the southeastern United States, parts of the Southwest and California, *Ae. albopticus* has a broader potential to spread the disease given its presence in the southeastern and mid-Atlantic states as well as parts of the Southwest, Northeast, and lower Midwest. Similarly, the extensive degree of human travel between the Americas for sun worship and commerce combined with mosquitoes hitching rides on commercial freighters and aircrafts promotes the inevitable spread of this disease, similar to the projected future distribution of Zika virus.

Clinical symptoms from a ChikV infection manifest quickly, with an average incubation of two to four days (range one to 14 days). Typical symptoms include high fevers for three to five days, polyarthralgias within a few days of fever, and a macular or maculopapular rash in many patients. Some also develop terrible headaches, myalgias, and gastrointestinal symptoms. More rarely, patients develop respiratory failure, cardiovascular decompensation, myocarditis, acute hepatitis, renal failure, and neurologic involvement (*e.g.,* meningoencephalitis, Guillain-Barré syndrome).

Typical joint involvement includes hands, wrists, and ankles; however, many also describe other arthralgias and axial skeletal involvement. Many patients have periarticular

edema, swelling, and/or large joint effusions. Over time, chronic ChikV features include persistent arthralgia/arthritis, edematous polyarthritis of fingers and toes, and/or severe tenosynovitis. *Chikungunya* is Swahili for "that which bends up" or "stopped walk", which accurately depicts the posture many acquire due to the severe pain from this disease.

The problem with ChikV is the great potential for more chronic, post-ChikV chronic inflammatory rheumatism (CIR), with development of nonspecific post-viral arthritis, RA, seronegative spondylitis, and other non-inflammatory musculoskeletal complaints including persistent arthralgia. A recent systematic literature review found that 25% of ChikV cases would develop post-ChikV CIR and 14% develop a chronic arthritis. The duration of these symptoms can vary considerably. In the majority of cases, NSAIDs and steroids are used first-line with associated physical therapy for affected joints. With more persistent and debilitating disease, traditional disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate and biologic agents such as TNF-inhibitors have been used with varying success.

Antiviral agents such as ribavirin and interferon-α may work in vitro, but do not combat the infection in humans. Similarly, antimalarials are not effective, even though some clinicians postulate that they have an anti-inflammatory effect. The persistence of ChikV in those with chronic disease has been questioned, as well as whether those affected individuals have immune dysregulation. Unfortunately, no current vaccine exists for ChikV. Recommendations are largely preventative, meaning avoid mosquito bites. Effective preventative methods include the use of screens, bed nets, avoidance of standing water, and use of insect-repelling products including Deet or Picaridin.

The case presentation above was my first experience with a patient with ChikV arthritis. While this gentleman likely represents a minority of post-ChikV-CIR patients, the profound pain and functional impairment is difficult to forget. Some patients who present with post-ChikV CIR have a premorbid status of other musculoskeletal complaints (*e.g.,* osteoarthritis) and these symptoms can be amplified as well. Cohorts reporting post-ChikV-CIR from different areas around the world may vary in the degree of musculoskeletal complaints, possibly reflecting differences in viral strains and joint effects in the local population.

While post-ChikV-CIR patients currently make up only a tiny portion of inflammatory arthritis (IA) patients in our practice, there remains the question of whether we can truly lump these patients into an inflammatory group. It is important to keep ChikV in mind in those patients with a history of travel to higher-risk countries. Confirming the diagnosis may have an impact on prognosis for the patient and how quickly one pursues the IA treatment paradigm. Moreover, a significant percentage of patients may improve and not require DMARDs, but rather supportive NSAIDs and the tincture of time. On a cautionary note, post-ChikV-CIR prevalence may increase, thanks to the contributions of the mosquito vectors and climate change.

Image courtesy of Centers for Disease Control and Prevention. Available at: *www.cdc.gov/chikungunya/fact/index.html*.

Suggested Readings
1. Wilson ME. UpToDate: Chikungunya fever. April 13, 2016. Available at: *www.uptodate.com/contents/chikungunya-fever.*
2. Rodriquez-Morales AJ, Cardona-Ospina JA, Fernanda Urban-Garzon S, et al. Prevalence of post-Chikungunya Chronic Inflammatory Rheumatism: A Systematic Review and Meta-Analysis. Arthritis Care Res (Hoboken). 2016 Mar 25. [Epub ahead of print].
3. Zeana C, Kelly P, Heredia W, et al. Post-chikungunya rheumatic disorders in travelers after return from the Caribbean. Travel Med Infect Dis 2016; 14(1):21-5.

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