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Brief Report

Chronic Arthritis in Chikungunya Virus Infection[☆]

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ABSTRACT

Introduction: Chikungunya virus infection causes arthralgia and arthritis in the acute phase of the disease but, in more than half of the cases, musculoskeletal manifestations can be prolonged over time and, in some cases, become chronic. Although polyarthralgia is the most frequent chronic manifestation, forms with polyarthritis, tenosynovitis and enthesopathy are also common.

Objective: To analyze the clinical characteristics of patients with persistent articular manifestations after infection with the Chikungunya virus.

Patients: Report of 3 cases of chronic arthritis after infection with Chikungunya virus diagnosed at out-patient care in a university hospital of Catalonia, all of them imported after exposure in areas of epidemic infection between 2013 and 2015.

Results: All three patients had inflammatory joint pain for more than one year after acute disease (3, 2 and 1 years, respectively). In all cases, it appeared as polyarthritis with involvement of small joints of hands and feet (pseudorheumatoid arthritis-like). Laboratory tests showed a slight elevation of acute phase reactants, and analyses for immune markers were negative. Two of the patients required treatment with glucocorticoids and hydroxychloroquine. The course led to slow clinical improvement, but only one of them came to be completely asymptomatic.

Conclusion: In the differential diagnosis of chronic polyarthritis, Chikungunya virus disease should also be considered in areas in which it is not endemic.

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Artritis crónica en la infección por virus de Chikunguña

RESUMEN

Introducción: La infección por virus de Chikunguña ocasiona artralgias y artritis en la fase aguda de la enfermedad, pero en más de la mitad de los casos las manifestaciones musculoesqueléticas pueden prolongarse en el tiempo y en algunos casos se hacen crónicas. Aunque la poliartalgia es la manifestación crónica más frecuente, también son comunes las formas con poliartritis, tenosinovitis y entesopatía.

Objetivo: Analizar las características clínicas de los pacientes con manifestaciones articulares persistentes tras la infección por virus de Chikunguña.

Pacientes: Presentamos 3 casos de artritis crónica tras infección por virus de Chikunguña diagnosticados en las consultas de reumatología de un hospital universitario de Catalunya, todos ellos importados tras exposición en zonas de infección epidémica entre 2013-2015.

Resultados: Los 3 pacientes presentaron clínica articular inflamatoria durante más de un año tras la viriasis (3,2 y un año, respectivamente). En todos los casos en forma de poliartritis con predominio de afectación de pequeñas articulaciones de manos y pies (patrón pseudoartritis reumatoide). En las pruebas de laboratorio se observó leve elevación de los reactantes de fase aguda, con negatividad de los marcadores

Palabras clave:

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inmunitarios. Dos de las pacientes precisaron tratamiento con glucocorticoides e hidroxiquina. La evolución fue hacia una lenta mejoría clínica, pero tan solo una de ellas quedó totalmente asintomática. **Conclusiones:** En el diagnóstico diferencial de la poliartritis crónica se debe considerar la enfermedad por virus de Chikunguña, no solo en las zonas endémicas.

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Introduction

Chikungunya virus is an alphavirus (family *Togaviridae*) that is transmitted to humans by the *Aedes* mosquito. It causes an acute febrile disease with polyarthralgia, that is frequently severe and disabling. It was discovered in Tanzania in 1952 and initially produced sporadic epidemics in Africa and Asia, but in 2005, the virus became capable of mutation, which also enabled it to be transmitted via the *Aedes albopictus*, a mosquito distributed all over the world. Since then, there have been a number of epidemics in Africa, Southeast Asia and the islands of the Indian Ocean and Europe. The first autochthonous transmission in tropical America was identified at the end of 2013. Soon after, there was a severe outbreak in the majority of the Caribbean islands, which has now reached the north of South America and the United States. At the present time, the disease produced by this arbovirus creates an important public health problem in large areas of America and Europe that are colonized by this mosquito.¹

The joint manifestations, in both the acute and chronic phases, have a fundamental role in the presentation of the disease. Thus, rheumatologists in regions in which the disease is not endemic should also take it into account, particularly because of the capacity of this virus to induce different forms of chronic rheumatism.²

Acute infection is characterized by high fever and extremely severe polyarthralgia, after an incubation period of 2–7 days. The joints most widely affected are those of the fingers, carpi, ankles and knees. Myalgia is also common, as is tiredness, general poor health, gastrointestinal symptoms and a rash, generally a maculopapular eruption on the torso, face and limbs, that occasionally is pruriginous. This acute phase of the disease usually lasts from 7 to 10 days, although it can reach up to 3 weeks.³

Fourie and Morrison reported the first syndrome of post-Chikungunya rheumatoid arthritis in 1979 and, in 1983, Brighton et al. stressed the high prevalence of chronic polyarthralgia or joint stiffness that developed some 3 years after the onset of the disease. The proportion of patients with chronic symptoms decreases with respect to the time of infection (from 100% to 88% during the first 6 weeks, to 50% after 3–5 years). The majority is in the form of symmetric polyarthralgia, but frequently there is also joint swelling and chronic myalgia. The joints most widely affected in this phase are the knees, ankles and the small joints of hands and feet. However, the chronic phase is also accompanied by pain in proximal and axial joints, a situation that is not observed in the acute phase.

We report 3 cases of chronic arthritis after infection by Chikungunya virus diagnosed in the rheumatology department of a teaching hospital in Catalonia, in Spain, all of which had been imported after exposure in areas of epidemic infection between 2013 and 2015 according to diagnostic criteria.⁴

Patients and Results

Case no. 1. The patient was a 33-year-old Spanish woman; she was a health care professional and had no relevant medical history. In 2013, while on a trip to Southeast Asia (Indonesia), she developed acute-onset high fever (39 °C), generalized nonpruritic rash and severe polyarticular pain with substantial mobility limitation. The fever disappeared over the following week, as did the rash, but

the generalized joint pain continued to be severe and limiting, and she did not respond to treatment with paracetamol or nonsteroidal anti-inflammatory drugs (NSAID). Over the next 4 weeks the joint pain became focused on the carpi, small joints in the hands, ankles and feet, with morning stiffness in these joints that lasted more than an hour. At that point, she came to the rheumatology department.

The physical examination revealed symmetric arthritis of the carpi, in certain metacarpophalangeal joints (MCP), ankles and metatarsal joints (MTP). She felt pain associated with the mobility of shoulders and knees, with no sign of joint effusion. She underwent gray-scale ultrasound of the joints of hands and feet, that confirmed the presence of mild synovitis in both carpi, with a grade 2 Doppler signal. We also saw signs of active synovitis in the 2nd and 3rd MCP and MTP of both feet. Other imaging studies were normal. Laboratory tests showed a normal complete blood count, C-reactive protein (CRP) was 2.86 mg/L, erythrocyte sedimentation rate (ESR) was 21 mm/h, aspartate aminotransferase was 27 IU/L, alanine aminotransferase was 42 IU/L, normal complete blood count. Serological tests for Chikungunya virus using indirect immunofluorescence (enzyme-linked immunosorbent assay [ELISA]) were positive for IgG and IgM (Instituto de Salud Carlos III, Madrid, Spain). Tests for dengue were negative. Determinations for rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, antinuclear antibodies (ANA) and human leukocyte antigen (HLA) B27) were negative, as were serological tests for hepatitis B and C virus.

She began treatment with methylprednisolone at 8 mg/day, with rapid improvement in the clinical manifestations. After gradual tapering over the next 8 weeks, the complete interruption of the glucocorticoids was attempted, but joint pain rapidly reappeared, with limitation of her daily and professional activity. Her analyses showed a moderate elevation of acute-phase reactants. Over the following months, she alternated periods in which she required low-dose glucocorticoids or NSAID, but we were unable to suspend treatment. She began hydroxychloroquine at 200 mg/day which she took for 6 months, but there was no improvement in the joint manifestations, and it was suspended. Over the last 24 months, she has continued to have episodes of intensification of joint pain in hands and feet, during which she took short cycles of methylprednisolone (4 mg/day) or an NSAID. It was proposed to initiate treatment with methotrexate, but the patient rejected it because of the rapid response to glucocorticoids and her hope to soon become pregnant. At the present time, she has no signs of active synovitis according to ultrasound, although it has been confirmed that the joints of her hands and feet are involved in each of the inflammatory flares. Radiological follow-up has shown no development of erosions.

Case no. 2. The patient was a 40-year-old woman from Brazil, with no significant medical history until she developed Chikungunya fever in her country in December 2014, in the setting of an epidemic outbreak in the area in which she lived (temperature >38 °C, rash and polyarthralgia). In February of 2016, she was admitted to the rheumatology department of our hospital, after being referred from the unit of tropical infectious diseases, for evaluation of the polyarthralgia. The patient mentioned joint pain with the onset of a febrile episode, 14 months earlier, that had persisted since then. The pain mainly affected small joints in her hands and

feet, but was also noted in her shoulders, knees, ankles and hips. She had morning stiffness that lasted about 15 min, with no other systemic manifestations, with the exception of an excessive loss of hair in recent months. Her primary care physician had indicated treatment with dexamethasone in April of 2015, with initial doses of 24 mg/day, to be tapered to 2 mg/day in December of 2015. The joint manifestations improved, but she developed a cushingoid habitus. Since then, she is being treated with indomethacin.

The examination revealed arthritis in the MTP of both feet, pain on palpation of the carpi and proximal interphalangeal joint PIP of both hands and pain upon mobility of her shoulders. The ultrasound study revealed active synovitis in right carpus (grade 2 Doppler signal) and MTP (grade 1 Doppler signal). Laboratory tests showed a normal complete blood count, ESR and CRP, whereas the determinations of RF, anti-CCP, ANA and HLA-B27 were negative. Radiographs of her hands and feet were normal. Treatment with NSAID was maintained and hydroxychloroquine (200 mg/day) was added. There was an improvement in the joint manifestations after 3 months and, thus, the treatment has been continued.

Case no. 3. The patient was a 25-year-old woman who consulted our department for polyarthralgia. A year before she had been diagnosed with Chikungunya disease in the Dominican Republic. She had fever ($>38^{\circ}\text{C}$), a cutaneous eruption and polyarthralgia, that developed in the epidemiological setting of a local outbreak, but there was no serological confirmation. The arthralgias persisted and the origin of the pain was inflammatory. It predominated in her hands (with difficulty in extending her fingers) and her knees. Joint ultrasound, performed in the office, showed no synovial swelling or Doppler signal in the joints of the carpi, MCP or PIP. There were no signs of disease in the diverse tendon compartments of the hands. Laboratory tests showed a normal complete blood count, ESR of 27 mm, CRP of 0.2 mg/L, positive RF at a low titer (16.9; normal <14). The examination revealed arthritis in left carpus, pain in MCP of both hands and MTP of both feet. The determination of anti-CCP, ANA and serological tests for parvovirus were negative, although the serology for Chikungunya virus with ELISA was positive for IgG and was not detectable for IgM. Serological test for dengue was negative. The clinical outcome tended toward a gradual improvement of the joint manifestations, and the patient is only taking a NSAID. After an 18-month follow-up, no recurrence of the arthritis has been observed.

Discussion

Musculoskeletal manifestations of Chikungunya virus infection can be prolonged over time and become chronic in 40%–80% of the patients. We report 3 cases diagnosed in a region in which the disease was not endemic, in the setting of a study of polyarthritides. Although polyarthralgia is the most frequent chronic manifestation, forms with polyarthritides, tenosynovitis and enthesopathy are also common. Morning stiffness, myalgia and edema of the upper and lower limbs have also been described many months after the acute infection.⁵

Analytical studies can demonstrate elevation of inflammatory reactants and lymphopenia is frequently observed during the acute phase of the disease.^{6,7} In contrast, cytopenias do not usually develop during the chronic phase of the joint symptoms, as in the cases presented here.

Radiographic lesions were found in half of the patients with chronic arthritis in a cohort of 159 patients on Reunion Island.⁸ Between 3 and 4 years after the onset of the infection, the radiographic lesions that developed more often had the clinical features of post-Chikungunya rheumatoid arthritis (80%) than those of spondyloarthritis (40%) or undifferentiated arthritis (10%).

Chikungunya virus infection very frequently induces mixed cryoglobulinemia, as well as hepatitis C virus. The presence of cryoglobulins has been detected in up to 55% of the patients after the first year of the disease; their presence has been related to the persistence of arthralgia, although we have failed to observe other characteristic signs of cryoglobulinemia, such as palpable purpura or other manifestations of small vessel vasculitis. There have also been reports of Still's disease and catastrophic antiphospholipid syndrome associated with Chikungunya fever, which trigger a macrophage-mediated cytokine storm.

There have been descriptions of neurological manifestations such as encephalitis (11%), meningoencephalitis (2%), seizures (2%) or Guillain-Barré syndrome (1%). Hepatitis, myocarditis and diverse forms of ocular conditions have also been reported.

The pathophysiology of chronic joint involvement is not clear. The humoral response during the acute phase of the infection is primordial for eliminating the virus and preventing chronic disease. There are data that point to the presence and persistence of RNA of the virus in joint tissues, but the viral burden during the acute phase can also be a determinant of the immune-mediated chronic reaction induced by macrophages, T cells and natural killer cells.

The existence of risk factors that are conducive to chronic joint disease have not been consistently identified.

Treatment during the acute phase is based on rest, hydration, NSAID and analgesics. The response to NSAID is frequently poor^{8,9} and low-dose glucocorticoids are administered to 70% of the patients with disabling joint involvement or in the presence of severe extra-articular complications. Hydroxychloroquine and methotrexate have been utilized in chronic joint manifestations, with better results with the latter. Its use should be reserved for patients with clinical signs of chronic joint disease, and should be avoided during the acute phase of the infection.¹⁰

There is little evidence of the efficacy and safety of anti-tumor necrosis factor drugs in the treatment of this arthritis. On the other hand, in the Dominican Republic, a group of authors reported 53 cases of Chikungunya virus infection during the follow-up of a cohort of 328 patients with rheumatoid arthritis who were taking biological therapy,⁹ and none of them required modifications in the treatment, a fact that indicates the safety of its utilization in that situation.

In Spain, there have been reports of imported Chikungunya fever, but none have resulted in the chronicity of clinical manifestations involving the joints.¹¹

In conclusion, rheumatologists should incorporate this etiology into the study of polyarthritides lasting for more than 6 weeks, and always take into account issues with respect to epidemiological risk, even in regions in which the disease is not autochthonous.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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