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Case Report

Methotrexate for Chronic Chikungunya Arthritis

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ABSTRACT

Chikungunya Fever (CHIKF) is an acute febrile illness caused by the Chikungunya Virus (CHIKV), characterized by high fever, polyarthralgia / arthritis, headache and maculopapular rash. CHIKV has the potential to progress to Chronic Chikungunya Arthritis (CCA). Manifestations of CCA are varied, but some patients meet classification criteria for other rheumatic diseases, including Rheumatoid Arthritis (RA), fibromyalgia or spondylo arthritis. Not only does CCA "mimic" RA clinically, but there are similarities in pathogenesis, evidenced by cytokine and inflammatory modulator expression in these diseases. Although CHIKV was isolated in 1952 and CHIKF been known for decades, there is still no standard therapy for CCA. We report a patient who developed CCA with clinical features similar to RA, persisting for two years after CHIKV infection. In this patient, Methotrexate (MTX) was rapidly effective, suggesting a disease modifying mechanism of action similar to the effect in RA.

INTRODUCTION

Chikungunya Virus (CHIKV) is an alpha virus in the Togaviridae family, transmitted by Aedes mosquitoes, mainly Aedes aegypti in Africa, the Americas and Asia, and Aedes albopictus in the islands of the Indian Ocean and Europe [1,2]. CHIKV is an envelope, single-stranded RNA-virus of ~ 60-70 nm in diameter [1,2]. It was first isolated in 1952 in Tanzania. Since then large outbreaks have been reported in Africa, Asia, Europe and the Americas, where it resurfaced in 2013, including Brazil in 2014 [2,3].

The illness expresses itself in two phases. After a 4-7 day incubation period, CHIV causes an acute, febrile illness in up to 95% of cases, called Chikungunya Fever (CHIKF), characterized by high fever, disabling polyarthralgia and symmetric polyarthritis, headache and maculopapular skin rash, sometimes also associated with diarrhea, vomiting, myalgia, asthenia and lymphadenopathy [4]. It should be noted that recently high rates of asymptomatic infection have also been recorded in Thailand (47.1%) and Kenya (45.1%) with east/central/south African viral lineages [5].

Following CHIKF, greater than 40% of patients develop chronic inflammatory rheumatic symptoms, including painful arthralgia and frank arthritis [6]. The duration of these symptoms varies from days to months to years. The pathogenesis of Chronic Chikungunya Arthritis (CCA) is uncertain. Proposed hypotheses include persistence of a low level of replicative virus in the joints, persistence of viral RNA in synovium and induction of autoimmunity. Pro-inflammatory cytokine / chemokine responses, including high levels of IL-6, GM-CSF, IFN-⟨, and IL-17, are similar to the profile seen in Rheumatoid Arthritis (RA) [5,7,8].

No specific antiviral treatment has been shown to be effective against CHIKV. Treatment during the acute phase of CHIKF consists of supportive therapy [9]. Patients with CCA have been treated with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids, Hydroxychloroquine (HCQ), Sulfasalazine (SSZ), Methotrexate (MTX), and biologic agents, alone or in combination [3,6]. CHIK has become an epidemic illness throughout the tropical and subtropical world, including Brazil [3], and CCA occurs with high frequency. Effective therapy is urgently needed. We recently evaluated currently available treatment for CCA [10]. The most promising agent for CCA is MTX; although available evidence is limited [11]. We now report a CCA case, effectively treated with MTX that supports the use of MTX in CCA.

CASE PRESENTATION

A 50 years old woman, residing in Pernambuco, Brazil, developed high fever, incapacitating and symmetrical arthritis of the hands, wrists, knees and ankles. She also had headache, maculopapular rash and myalgia that lasted 7 days. Based on her symptoms and residence in an epidemic region, CHIKF was suspected by her primary care provider. She was treated with dipyrone and paracetamol. Her symptoms resolved after 3 weeks.

She remained asymptomatic for one year. She then developed painful, symmetrical arthralgia of the hands, wrists, knees and ankles. These symptoms persisted throughout the next year. Two years after the onset of CHIKF, she presented to one of us with arthritis in Proximal Interphalangeal (PIP) joints of the hands, metacarpophalangeal and wrists; deformity in the PIP joint of the 3rd finger of the right hand and the 2nd finger of the left hand (Figure 1).

Figure 1: 3 years after CHIKF, A 50-year-old women had ongoing arthritis in hands and wrists.

Assessment of the severity of her arthritis included the Visual Analog Pain Scale (VAS). The patient reported that her pain was 10 out of 10. Tender and swollen joint counts were 10 and 10, respectively. Disease Activity Score (DAS) 28-ESRwas 6.46. The laboratory investigations revealed normal complete blood count, erythrocyte sedimentation rate (ESR)31 mm/h, C-reactive protein (CRP) 48 mg/L, aspartate transaminase 20 mg/L, alanine aminotransferase 18 mg/L, rheumatoid factor 64 µl/ml, CHIKV ELISA serology IgG: reactive, IgM: non-reactive,(kit EUROIMMUN).

She was diagnosed with CCA and received MTX 15 mg / week and folic acid 5 mg / week. After 4 weeks, the patient reported that her pain was 1 out of 10 (VAS). Tender and swollen joint counts were 2 and 0, respectively (Figure 2). DAS 28-ESR had fallen to 3.03, with ERS 20 mm/h and CRP 6 mg/L. Treatment was well tolerated. Laboratory monitoring, including post-treatment complete blood count, liver function tests, and creatinine were normal.

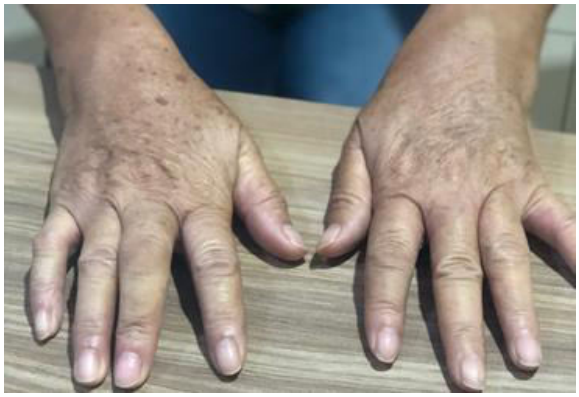

Figure 2: The patient responded to 4 weeks of treatment with MTX 15 mg/week.

DISCUSSION

CHIKV infection is followed by chronic rheumatic disease in a variable proportion of patients [6]. In a Colombian study of 152 patients with CHIKF, persistent rheumatologic symptoms occurred at 26 weeks in 53.7% and joint edema was present in 40.6% [12]. An Indian study of 437CHIKF patients reported that 57% developed post-viral polyarthralgia, 22% inflammatory polyarthritis, and 19.5% tenosynovitis during a 15-month period [13]. After the 2014–2015 outbreak of CHIKF in the US Virgin Islands, one study of 88 subjects

documented chronic arthritis in 47% of infected individual's at 24 months [14].

Javelle et al. evaluated 159 cases of CHIKV arthritis in which symptoms were present for at least 2 years. They characterized clinical patterns of arthritis in112 individuals with chronic inflammatory rheumatism; 33 patients fulfilled criteria for spondyloarthritis (European Spondyloarthropathy Study Group [ESSG] Classification), 40 for RA (2010 American College of Rheumatology/European League against Rheumatism [ACR/EULAR] criteria), and 21 for undifferentiated polyarthritis [15]. In a cohort of American missionaries in Haiti, Miner et al. reported that 8 of 10 CHIK infected patients with arthritis fulfilled ACR/EULAR 2010 criteria for seronegative RA [16].

Recently, we evaluated a cohort of 50 Brazilian patients seen in our clinic with Chronic Chik Arthritis (CCA) that we defined as arthritis/arthralgia persisting for more than 3 months after the onset of CHIKF. Thirty of our patients (60%) had arthralgia while 20 patients (40%) also had arthritis, with clinically evident synovitis. Of the patients with arthritis, all 20 had hand involvement. Other joints with arthritis were wrists in 16 (32%), ankles in 12 (24%), and ankles and knees in 9 (18%). ACR criteria for RA were met by 11 (22%) of the patients [17].

The pathogenesis of CCA is not well understood, but there are intriguing similarities in immunological responses of peripheral blood mononuclear cell of patients with RA and CCA. One hypothesis that has been proposed to explain CCA is the induction of autoimmunity [18]. In some studies, CCA is associated with high circulating levels ofIL1, IL-5, IL-6, GM-CSF, IFN-α, IL-10, and particularly IL-7and IL-15, similar to the cytokine signature seen in RA [17]. In a study of the inflammatory cytokines and chemokines in CCA, plasma levels of IL-6 and GM -CSF were significantly higher in patients with persistent arthralgia compared with those who had recovered [19]. IL-6 is involved in the joint pain associated with RA and increases the production of cartilage-destroying enzymes [2].

CCA can cause joint damage, bone erosion, and worsening of the quality of life as severe as occurs in RA and related diseases [20]. MTX exerts an anti-inflammatory effect through inhibition of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, GM-CSF and TNF. Because of this anti-inflammatory mechanism and because of the clinical similarities between CCA and RA, including the risk of irreversible joint deformity, there has been growing interesting the use of MTX in CCA patients [5,11,15,17]. We treated our patient with MTX 15 mg /week. Within 4 weeks, we observed a satisfactory improvement in joint pain and edema. We also calculated meaningful improvement in VAS and DAS28-ESR during this period [21].

CONCLUSION

A high proportion of patients with CHIKV infection may develop RA-like chronic rheumatic disease and could benefit from therapy similar to treatment of RA. In this article, we present a case report of successful MTX treatment in a patient with CCA. The therapeutic response was rapid, effective and well tolerated. There is a need for larger-scale, statistically rigorous, placebo-controlled, randomized prospective studies of MTX monotherapy in CCA, evaluating safety and efficacy, using quantifiable outcome measures such as the DAS28-ESR.

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