

Acute chikungunya fever followed by systemic lupus erythematosus

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Chikungunya virus may need to be added to the list of viruses that “trigger” systemic lupus erythematosus.

Chikungunya fever (CHIKF) is a viral disease caused by the chikungunya virus (CHIKV), a single-stranded positive-sense RNA virus in the *Alphavirus* genus of the *Togaviridae* family. Like many other arboviral diseases, it is transmitted by mosquito vectors, primarily *Aedes aegypti* and *Aedes albopictus* [1]. The acute illness lasts 5-14 days and is characterized by abrupt fever, debilitating polyarthralgia/polyarthritis, maculopapular rash, myalgia and headache [2]. More than 40% of CHIKF patients develop arthritic manifestations lasting more than 3 months, called chronic chikungunya arthritis (CCA). CCA typically causes symmetrical polyarthritis affecting the hands and feet similar to rheumatoid arthritis (RA), non-specific arthralgias consistent with post-viral arthritis or asymmetric oligo or mono arthritis similar to seronegative spondyloarthritis (SpA) [3].

Systemic lupus erythematosus (SLE) is a chronic systemic disease with a wide variety of clinical manifestations, including arthritis. Autoimmunity clearly plays a role in SLE, but many aspects of its pathogenesis are unclear [4]. Infections may contribute to the pathogenesis of SLE and several pathogens, including the Epstein-Barr virus (EBV), parvovirus B19 virus, exogenous retroviruses (eg, human type 1 lymphotropic virus [HTLV-1] and human immunodeficiency type 1 [HIV-1]) and endogenous retroviruses (ERVs) have been implicated [5]. We report two female patients, both previously asymptomatic, who developed SLE soon after CHIKV infection.

In 2016, during an outbreak of CHIKF in Pernambuco, Brazil, a 37-year-old woman (case 1) developed fever, severe arthralgia, myalgia and maculopapular rash consistent with CHIKF. Four months later, she had continuing arthralgia, accompanied by malar rash, fatigue, hair loss and photosensitivity. This illness persisted for 2 years at which time she was seen by us. We confirmed CHIKV infection by ELISA (Table 1). In addition, the patient fulfilled 2019 EULAR/ACR classification criteria for SLE (antinuclear antibodies [ANA] at a titer of $\geq 1:80$, joint involvement, malar rash, anti-dsDNA positive, non-scarring alopecia, leukopenia $< 4,000/\text{mm}^3$, low C3 and low C4) [6] (Table 1). She was treated with hydroxychloroquine 400 mg/day, methotrexate 15 mg/week, folic acid 5 mg/week and prednisone 5 mg/day. She responded well to therapy over 2-year follow-up with improvement of symptoms.

In October, 2019, during an epidemic of CHIKF in Pernambuco, Brazil, a 15-year-old girl (case 2) developed disabling polyarthritis, fever, malaise, headache and fatigue. Over 2 months, she had weight loss and lack of appetite. Recent CHIKV infection was confirmed by ELISA (Table 1). In addition, the patient fulfilled 2019 EULAR/ACR classification criteria for SLE (ANA at a titer of $\geq 1:80$, fever, joint involvement, leukopenia, C3 and low C4, anti-dsDNA antibodies, proteinuria $> 0.5 \text{ g}/24 \text{ hours}$) [4,6]. We treated her with hydroxychloroquine 400 mg/day and prednisone 20 mg/day. In February 2020, she developed lupus nephritis (persistent proteinuria $> 0.5 \text{ gm per day}$ and/or cellular casts including red blood cells, hemoglobin) [5] (Table 1).

A number of reports characterize CCA as “post-chikungunya chronic inflammatory rheumatism (CIR-CHIK)” [7]. Javelle et al. described 159 patients who were symptomatic for at least 2 years, 112

Time line	Patient 1 Age 37 years Female				Patient 2 Age 15 years Female			Normal range
	Apr 2018	Jun 2018	Nov 2018	Jul 2019	Nov 2019	Dec 2019	Feb 2020	
White cell count, cell/mm ³	2,300	2,500	4,640	4,100	3290	4840	3690	4,500-11,000
Neutrophils	1,700	1,840	2,500	2,500	1,700	2,250	2,740	1,570 -7,700
Hemoglobin, gm/dl	10.8	11.8	12.5	13	12	10.1	10.3	12-16
Platelet count, per mm ³	105,700	112,000	209,000	207,000	196,000	276,000	232,000	150,000-450,000
Mean corpuscular volume, mm ³	81	83	91	80.3	92	81.2	88	80-100
ESR, mm/hour	30	15	14	14	N/R	20	55	< 20
C-reactive protein mg/dl	6	N/R	N/R	N/R	N/R	N/R	N/R	< 6
RF, IU/ml	N/R	-	-	N/R	N/R	N/R	N/R	< 30
Anti-CHIK IgM	N/R	-	-	-	-	4.6	-	N/R
IgG	2.53	-	-	-	-	88	-	N/R
ANA (Hep 2 cell)	1:640 Nuclear dense fine speckled	1:640 Nuclear dense fine speckled	-	1:640 Nuclear dense fine speckled	1: 1280 Nuclear fine speckled	-	-	N/R
Anti-Ro U	113.6	-	-	83	N/R	N/R	52	<20 N/R
Anti-La U	24	-	15	N/R	N/R	N/R	N/R	<20
C3 mg/dl	62	73	87	91	-	44	51	80-160
C4 mg/dl	8	8	13	17	-	8	8	16-48
CH50 U/CAE	6	15.4	32.8	42	-	5	9	60-265
Anti-Sm	N/R	-	-	N/R	-	N/R	N/R	N/R
Anti-dsDNA	1:80	-	N/R	N/R	-	1:80	1:80	N/R
24-hour urine protein mg/day	-	-	28	-	-	150	1326	<200 mg/day
Urinalysis	NL	NL	NL	NL	NL	-	HB+,PT+, LKC++, mucus	NL

ANA: Antinuclear Antibodies; RF: Rheumatoid Factor; HB: Hemoglobin; PT: Protein; LKC: Leukocytes; Anti-CHIK: Antibodies Anti-chikungunya Virus; N/R: Non-reactive; NL: Normal.

Table 1: Laboratory tests of patients diagnosed with lupus after chikungunya virus infection.

of whom developed CIR-CHIK classified as mimicking 4 clinical patterns: RA, SpA, fibromyalgia or undifferentiated polyarthritis, defined as the presence of inflammatory arthritis affecting more than 4 joints of greater than 6 weeks duration in the absence of an alternative diagnosis [6]. Other reports have also focused on CCA as an “RA mimetic”. Among 203 patients with CHIKF who developed joint pain, 36% (34/94) met the ACR/EULAR criteria for RA [8].

It is hypothesized that viruses may cause or exacerbate pre-existing rheumatic diseases. For example, parvovirus B19 infection can mimic SLE clinically and could play a role in the pathogenesis of SLE. Similarly, hepatitis C virus infection may share clinical and serologic features with SLE, polyarteritis nodosa, sarcoidosis, and Sjögren’s syndrome (SS). Extrahepatic manifestations of hepatitis C virus such as arthralgia, myalgia, sicca syndrome, and antinuclear antibody (ANA) positivity can also mimic SLE. Many studies have linked EBV to the development of systemic SLE, RA, and SS, in part because several immune escape mechanisms and immunomodulatory proteins have been described for EBV [3]. In SLE, infectious agents may play an essential role in individuals with genetic predisposition. Infection may serve as a “trigger”, inducing aberrant innate and adaptive immunity. The latter may lead to loss of tolerance to autoantigens by mechanisms including molecular mimicry, epitope spreading, superantigen production, bystander activation, persistent viral infection, altered apoptosis and clearance deficiency and epigenetic factors [9].

A study suggests that the viral infections, particularly in endemic regions including Chikungunya viruses, trigger the development of autoimmunity (SLE) in genetically susceptible individuals [10]. Gupta evaluated 882 CHIKV-infected patients after an CHIKF outbreak. Of the total, 10 (6.99%) had rheumatoid arthritis (RA), 7 (4.89%) ankylosing spondylitis (AS), 3 (2.1%) psoriatic arthritis (PsA), and 2 (1.4%) SLE [11].

In this report, we present two patients who developed SLE after CHIK infection, possibly caused by mechanisms discussed above. CHIKV infection is an emerging global infection. It is estimated that 39% of the world’s population lives in countries endemic for CHIKV [3]. If CHIKV infection contributes to risk for SLE, this has important clinical and etiopathogenic implications. We believe that CCA may be a post-infectious, inflammatory process and that an understanding of the parallels and differences between CCA and other rheumatic diseases, including SLE, may offer insights into better diagnosis and treatment of both diseases.

Conflicts of Interest

None of the authors have any conflicts of interest.

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