CASE REPORT

Dengue and Chikungunya Co-infection Evolving into Systemic Lupus Erythematosus – Case Report.

Wahinuddin Sulaiman[1, 2], Dev Teo Cin Nee[2], Zakaria Abdul Kadir[2], Ahmad Helmi Abdul Karim[3], and Chun Lai Too[4].

[1]Faculty of Medicine Universiti Kuala Lumpur Royal College of Medicine Perak, No.3, Jalan Greentown, 30450 Ipoh, Perak, Malaysia.
[2]Department of Medicine, KPJ Ipoh Specialist Centre, Jalan Raja Di Hilir, Ipoh, Perak, Malaysia
[3]Department of Radiology, KPJ Ipoh Specialist Centre, Jalan Raja Di Hilir, Ipoh, Perak, Malaysia
[4]Immunogenetics Unit. Allergy and Immunology Research Center. Institute for Medical Research, National Institutes of Health Complex, Ministry of Health Malaysia, Setia Alam, Shah Alam, Selangor.

Corresponding Author
Dr Wahinuddin Sulaiman, MBBS, M.MED, FRCP
Faculty of Medicine, Universiti Kuala Lumpur Royal College of Medicine Perak,
No.3, Jalan Greentown, 30450 Ipoh, Malaysia.
Email: nwahin@gmail.com; wahinuddin@unikl.edu.my

Abstract

Viral infections are a common triggering factor in the initiation of autoimmune diseases. Dengue and chikungunya infections have been reported independently in the literature as triggering factors for patients who are predisposed to autoimmune diseases such as SLE. We report a 19-year-old girl who presented with dengue and chikungunya co-infection, subsequently manifested florid signs and serological markers of active SLE complicated by pneumonitis, hepatitis, and upper gastrointestinal hemorrhage. The co-infection of dengue and chikungunya fever was confirmed by positive test to dengue and chikungunya immunoglobulin M (IgM). Both dengue and chikungunya infections exhibit distinct clinical phenotypes but share a common mechanism of disrupting the immune system and triggering immune complex formation which predispose to the development of autoimmune diseases such as SLE. This was the first case we encountered where arboviruses co-infection evolved into SLE. It is important to learn from this complex case especially in our region where both dengue and chikungunya infections are endemic, considering the unfavorable outcome if improperly addressed and managed.

Keywords: dengue, chikungunya, co-infection, autoimmune disease, SLE.

Introduction

Dengue virus (DENV) and chikungunya virus (CHIKV) are single-stranded, positive-sense RNA viruses. Both are arthropod-borne viruses (i.e., arboviruses), sharing a common mode of transmission through different species of, *Aedes* mosquitoes i.e., Aedes *aegypti* as the principal vector and Aedes *albopictus* as a secondary vector.[1] Dengue fever has a high prevalence in Southeast Asia while chikungunya is endemic in Africa but spread to Asia and peninsular Malaysia, especially the west coast and the most recent outbreak was in the state of Perak. These infections usually overlap in endemic areas and have many common clinical features such as high-grade fever, rashes, nausea, headache and body pain. Thus, it is not always easy to differentiate the two infections clinically. Nevertheless, dengue infection may lead to different stages of manifestations and severity from mild to dengue shock syndrome and death. The common clinical manifestations of dengue infection include liver derangement and leucopenia. On the other hand, chikungunya mono-infection commonly causes debilitating arthritis requiring immunosuppressants. When there is co-infection by these arboviruses the clinical features and laboratory tests did not significantly affect the severity.[2]

SLE is a complex multisystem autoimmune disorder with a wide spectrum of clinical manifestations. There are multiple factors that may cause flare of SLE. It has been reported that dengue and chikungunya viruses may trigger the immune system leading to development of autoimmune diseases such as SLE.[3, 4] Dengue has been often reported in lupus patients to cause flare of the disease with unfavorable complications. We present a case of dengue and chikungunya co-infection that triggered SLE in a young girl complicated by clinically and serologically highly active disease with pneumonitis, hepatitis, severe pancytopenia and upper gastrointestinal bleeding.

Case report

A 19-year-old girl presented with history of intermittent low-grade fever for more than one month at the end of 2019 and she was diagnosed to have tonsillitis. In May 2020, she had patchy thick scaly rash on the scalp with alopecia which eventually improved. A month later, she had another episode of fever (39.3ºC) lasting for two weeks, dry cough and loss of weight. Clinical examination revealed a few vasculitis rashes on her digits of both hands. Initial laboratory tests showed bicytopenia (low hemoglobin and leucopenia) with raised ESR (72mm/hour) but normal CRP (Table 1). Her dengue nonstructural protein 1 (NS1) and anti-dengue virus Immunoglobulin G (anti-DENV IgG) were negative, but anti-DENV IgM and anti-chikungunya IgM (anti-CHIKV IgM) were positive indicative of recent infections. She was diagnosed as dengue and chikungunya fever with arthritis based on IgM positivity by ELISA. Polymerase chain reaction (PCR) for CHIKV RNA, all serotypes of DENV RNA; West Nile Virus RNA; Salmonella sp. DNA; Rickettsia sp. DNA; and Plasmodium sp. DNA were all negative.

She continued to experience low-grade intermittent fever, fatigability, myalgia, and arthralgia, and a month later, her vasculitis rashes worsened and SLE was suspected. At that juncture, her repeated ESR was markedly raised in contrast to CRP level with persistent leucopenia. Venereal disease research laboratory (VDRL) was positive at low titer, with negative Treponema pallidum hemagglutination (TPHA), and creatinine kinase (CK) was 302 U/L. Her double stranded-DNA autoantibody (dsDNA) was >200 U/L with ANA titer of 1:1280, with homogenous pattern.

SLE was not diagnosed until she presented a week later with worsening of vasculitis over the palms, malar regions and discoid rash, hair loss, fever, severe myalgia, arthralgia, fatigue, oral mucosal ulcers and poor appetite. During this episode, she

had menstrual bleeding which was heavier than usual. She had no other bleeding tendencies or thrombotic events. She also experienced headache which she claimed to be unusual. However, there was no neurological deficit. She had non-productive cough but no shortness of breath or chest pain. She did not have any significant urinary symptoms. She had no other past medical history of note. Her mother had four miscarriages during 2nd to 4th trimester pregnancies and was diagnosed to have small ovaries and fibroid was presumed to be the etiology. Clinical examination revealed vasculitis rash on the fingers of both hands, splinter hemorrhage, discoid rash in the external meatus of both ears, mild alopecia and oral ulcerations. She was febrile (37.9°C) with cracked lips. There was no bleeding tendency or evidence of thrombosis. Fine crackles were heard in the lower and middle zones of both lungs. Her laboratory test results are as shown in table 1. The hepatic transaminases were elevated. There was bicytopenia (low Hb and white cell count) at presentation followed by thrombocytopenia later. The rapid dengue antigen/antibodies detection by immunofluorescence-based method exhibited reactive IgM anti-DENV antibodies while anti-DENV IgG remained non-reactive, suggesting probably primary dengue infection or recent dengue infection. Plain chest radiograph shows reticular shadowing at lower and middle zones of both lungs suggestive of pneumonitis (Figure 1). Magnetic resonance imaging (MRI) of the brain revealed early vasculitis changes (Figure 2).

She was diagnosed with dengue and chikungunya co-infection triggering the development of SLE complicated by pneumonitis and hepatitis. Intravenous (IV) methylprednisolone 500 mg daily for three consecutive days and hydroxychloroquine 200 mg daily were given. Her clinical symptoms improved markedly.

However, a few days later she developed upper gastrointestinal (GI) hemorrhage and upper endoscopy revealed duodenitis. There was no evidence of disseminated intravascular coagulopathy (DIC). Two pints of blood (packed cells) were transfused since her hemoglobin level was low (9.1g/dL) and the platelet dropped from 20 x 103/uL to 17 x 103/uL. She showed marked improvement with normalizing of her platelet count without any further GI bleeding, resolving vasculitis and discoid rashes. The hepatic transaminases were normalizing as well. At discharge, she was prescribed oral prednisolone 60 mg daily and mycophenolate mofetil 500 mg twice daily. Her blood sample also tested negative for all dengue virus serotypes' RNA and chikungunya RNA prior to discharge. On her subsequent clinic visits, she was asymptomatic without active signs of SLE and her most recent treatment was prednisolone 10 mg and hydroxychloroquine 200 mg daily.

Discussion

Viral infections have been well documented as the main factor triggering autoimmune diseases. These infections result in a robust and usually well-coordinated immune response that is crucial for viral clearance. However, in some cases, the immune regulatory mechanisms may falter, culminating in the breakdown of self-tolerance, leading to immune-mediated attacks directed against both viral- and self-antigens, thus triggering autoimmunity. For instance, dengue has been known to be endemic in tropical countries and well described in previous reports as a trigger of autoimmune diseases such as SLE.[5-7] Dengue itself was not complicated or severe in patient with SLE due to the presence of IgG in sera of SLE patient which cross-neutralize dengue virus antibody.[8] In severe dengue, the autoimmune activation by cross reactivity of anti-NS1 and host proteins, endothelial cells, and platelets [9] lead to activated complement [10] and cause plasma leakage.

In Malaysia, chikungunya infection was first identified during an outbreak in Port Klang, Selangor in 1998, affecting more than 51 people.[11] Since then, chikungunya infection has become endemic in Malaysia spreading to many

states. Chikungunya infection is not generally fatal, and the symptoms of mild chikungunya infection subside spontaneously as the viral titer decreases in about 10 days.[12] Severe arthritis is the prominent clinical manifestation that can persist for months to years.

Dengue and chikungunya infections can co-occur since these two viruses share a similar geographical distribution and have a common transmitting vector i.e., *Aedes aegypti* mosquito. Unfortunately, their clinical manifestations also demonstrate substantial overlap. The infected patients with either virus typically present with acute onset of fever, myalgia, and headache. Some patients also experienced a maculopapular rash and gastrointestinal symptoms. Notably, fever, myalgia, arthralgia and thrombocytopenia are common findings in many diseases including SLE, rheumatoid arthritis, dengue, chikungunya and many other infections, which can lead to a diagnostic dilemma.[13] False-positive IgM for dengue has been reported in previous case reports [14] resulting in more diagnostic uncertainty especially in dengue and chikungunya endemic areas.

Till date, there is no report of SLE being triggered by co-infection of two arboviruses. i.e., dengue and chikungunya. Single arbovirus (dengue or chikungunya) has been implicated in previous case reports although co-infection with other conditions such as kikuchi's disease has been reported (Table 2). [5, 6, 15-18] This report describes the case of a patient with dengue and chikungunya co-infection, confirmed by positive results of IgM antibodies and presentation of SLE four weeks later. Multiple blood testing for IgG antibodies against the arboviruses remained non-reactive suggesting primary/recent viral co-infection.

The exact mechanisms between dengue, chikungunya and autoimmune diseases remain to be elucidated. Studies have reported that structural and non-structural proteins of viruses, e.g., dengue virus, share several molecular mimicries with platelets, endothelial cells, and coagulatory molecules, which may lead to cross-reactive autoantibodies. [8,16,19] Another possible mechanism by which viral infections could trigger autoimmune diseases is via epitope spreading, whereby the autoreactive T cells are activated due to tissue damage following viral infections, releasing self-epitopes because of the immune response.[20]

Conclusion

Co-infection is a matter of public health interest since they are transmitted by the same vector and may trigger the development of autoimmune diseases in susceptible individuals. Thus, it is important for clinicians to be familiar and thorough with various clinical presentations and laboratory assessment to make the diagnosis, initiate appropriate treatment and prevent the associated complications. The increasing frequency of dengue and chikungunya co-infection in endemic areas offers a new perspective in the immunopathogenesis of autoimmune disorders which may be the subject of future research.

Conflict of Interest

None

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Table1. Laboratory investigations during course of dengue and chikungunya co-infection and SLE development

Parameters	Normal range	Initial presentation with dengue and chikungunya co-infection (before SLE development)	2-week follow-up visit (post arboviral co-infection)	Development of SLE (4 weeks post arboviral co-infection); hospitalized	1-week post SLE diagnosis; discharged	2-week follow-up (post SLE diagnosis)	2-month follow-up (post SLE diagnosis)
Hb (g/dL)	11.5 – 16.0	9.8	9.7	9.4	10.0	12.0	11.9
WCC (x10^3/uL)	4.3 – 10.5	3.7	1.8	3	12.7	4.1	9.7
Neutrophil (%)	40 – 75	61.6	66.2	70.9	84.5	68.2	70.4
Lymphocyte (%)	20 – 45	34	27.3	23.4	11.3	21.8	22.8
Monocyte (%)	1 -- 11	3.6	4.9	5.7	4.0	10	5.5
Platelet (x10^3/uL)	150 - 450	202	206	20	356	356	405
Hct (%)	36 - 46	30	30	28	30	37.0	36.0
ESR (mm/1st hour)	0 - 25	72	86	74	-	-	-
CRP (mg//L)	< 5.0	1.54	3.67	14.2	-	0.51	1.54
ALT (U/L)	7 – 48	31	64	126	114	75	18
AST (U/L)	7 – 44	49	70	496	60.0	31	13
ALP (U/L)	<448	42	67	156	95	57	46
GGT	7 -- 42	23	127	171	546	239	41
Albumin (g/L)	35 - 50	40	39	32	34	44	43
CK (U/L)	24-173	-	-	302		-	-
Anti-CHIKV IgM	NR	reactive	reactive	-	-	reactive	-
Anti-DENV IgM	NR	reactive	-	reactive	-	-	-
Anti-DENV IgG	negative	negative	-	negative	-	negative	-
Anti-DENV NSI antigen	negative	negative	-	-	-	-	-
PCR for DENV, CHIKV	negative	-	-	-	-	-	-
PCR for COVID-19 / SARS-CoV-2 RNA	negative	Negative	-	-	-	-	-
VDRL	NR	-	Reactive (Titre 8)	-	-	-	-
TPHA	NR	-	NR	-	-	-	-
BT, (minutes)	<6.0	-	-	2	-	-	-
CT, (minutes)	5.0 -- 15.0	-	-	10	-	-	-
PT, (seconds)	11.0 -- 15.0	-	-	12.9	-	-	-
aPTT (seconds)	30-40	-	-	38.1	-	-	-
DAT	negative	-	-	++	-	-	-
IDAT	negative	-	-	+	-	-	-
INR	0.85 -- 1.35			0.99		-	-
RF (IU/mL)	<15	6.6	6.9	7.2	-	-	-
ANA	negative	-	-	1:1280 (Homogenous)	-	-	-
Anti-dsDNA (IU/mL)	<50	-	-	>200	-	-	-
C3 (g/L)	0.90-1.80	-	-	0.44	-	-	-
C4 (g/L)	0.15-0.45	-	-	0.10	-	-	-
Urinalysis	Normal	Normal	Normal	Normal	-	Normal	Normal

Hb, haemoglobin; WCC, white cell count; Hct, hematocrit; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALT, alanine transferase; AST, aspartate transaminase; ALP, alkaline phosphatase; CHIKV, Chikungunya virus; DENV, Dengue virus; PCR, polymerase chain reaction; COVID-19 RNA, 2019 Novel Coronavirus Ribonucleic acid; DENV, dengue virus; CHIKV, chikugunya virus; VDRL, Venereal Disease Research. Laboratory; TPHA, Treponema pallidum hemagglutination assay; BT, bleeding time; CT, clotting time; aPTT, activated partial thromboplastin time; DAT, direct antiglobulin test; IDAT, indirect antiglobulin test; INR, international normalized ratio; RF, rheumatoid factor; ANA, Anti-nuclear antibody; dsDNA, double stranded deoxyribonucleic acid; C3, complement 3; C4, Complement 4; NR, non-reactive.

Table 2. Dengue and Chikungunya associated with systemic lupus erythematosus case reports.

Ref.	Country	Age; sex	Clinical presentation	Arbovirus (DENV/CHIKV)	AID	Serological markers
Harris VK [15]	India	13, F	fever, skin rash and cervical lymphadenopathy	DENV and Kikuchi's disease	SCLE	DENV IgG +ve
Jardim DL [16]	Brazil	25; F	fever, myalgia, headache and petechiae, tender hepatomegaly and splenomegaly Serositis (pleural and pericardial effusion, ascites)	DENV	Unspecified AID	DENV IgM+ve ANA +ve, C3 low, Cryoglobulin +ve
Rajadhyaksha A [5]	India	22; F	fever, skin rash, dyspnea, retro-orbital pain, abdominal pain, arthralgias and myalgias	DENV	SLE, LN V	DENV IgM +ve ANA +ve Anti-dsDNA +ve C3, C4 low
Talib Sh [6]	India	32, F	fever, cough, epistaxis, and melena, dyspnea	DENV	SLE, LN IIIC	DENV NS-1 Ag (ELISA) +ve, ANA +ve, Anti-dsDNA +ve, C4 low, p-ANCA (IIF) +vw
Bercholc-Urinowsky IJ [17]	Mexico	13; F	fever, polyarthralgia, malar rash, photosensitive	CHIKV	SLE	CHIKV IgM +ve ANA +ve, anti-DNA-ENA +ve, anti-Sm +ve, aCL(IgM, IgG) +ve, C3 C4 low
Amaral JK [18]	Brazil	i)37; F ii)15; F	i)fever, severe arthralgia, myalgia, and maculopapular rash; malar rash, fatigue, alopecia, and photosensitivity. ii)polyarthritis, fever, malaise, headache, and fatigue	CHIKV	i)SLE ii)SLE, LN	CHIKV IgG +ve ANA +ve, anti dsDNA +ve, C3, C4 low.
This case	Malaysia	19; F	Fever, polyarthritis, malar rash, photosensitive, alopecia, pneumonitis, melena,	DENV and CHIKV	SLE	DENV IgG +ve, CHIKV IgG+ve, ANA+ve, anti-dsDNA +ve, C3C4 low

F, female; DENV, dengue virus; CHIKV, chikungunya virus; AID, autoimmune disease; SLE, systemic lupus erythematosus; LN, lupus nephritis; ANA, anti-nuclear antibody; dsDNA, double-stranded deoxyribonucleic antibody; C3, complement 3; C4, complement 4; ELISA, enzyme-linked immunosorbent assay; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibody; ENA, extractable nuclear antigen; aCL, anti-cardiolipin antibody; +ve, positive.

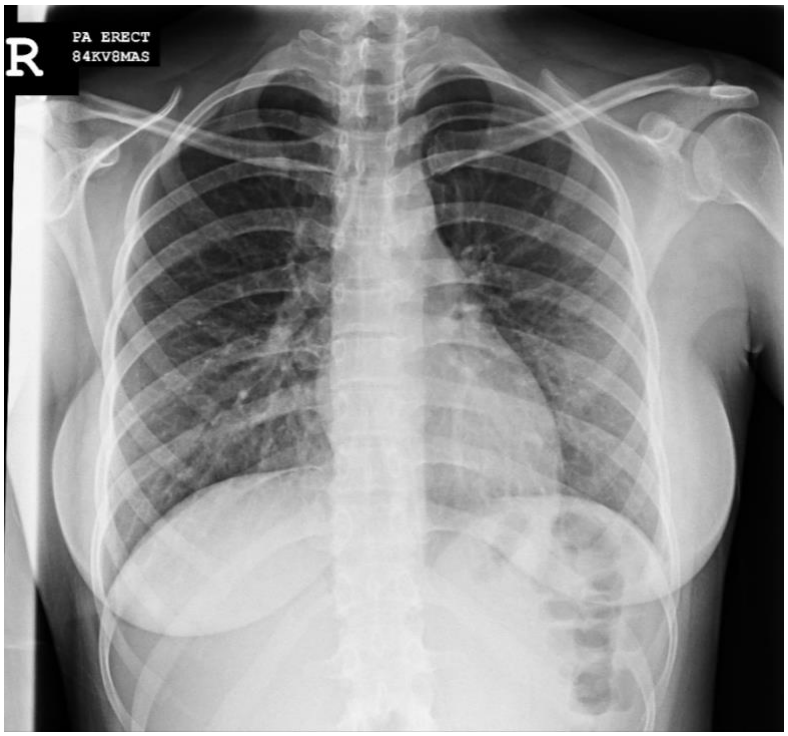

Figure 1. Plain chest radiograph showing mild haziness at the left lower zone suggestive of early pneumonitis.

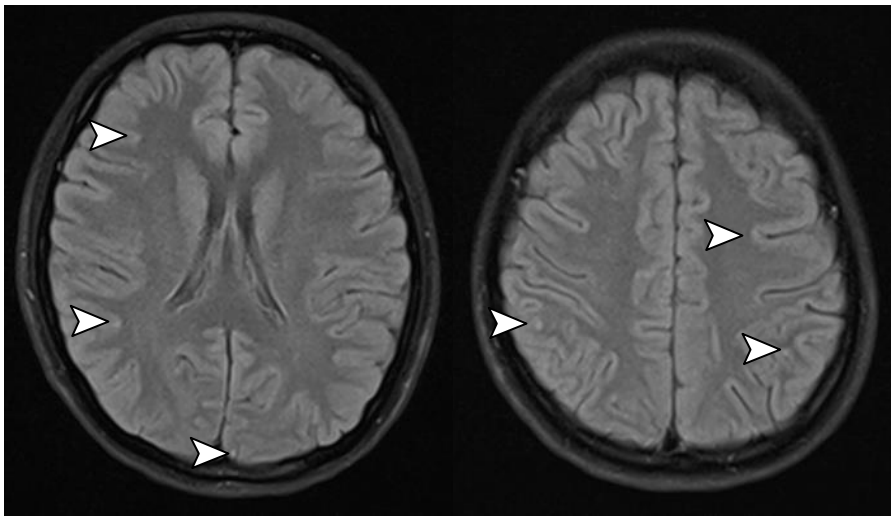

Figure 2. Magnetic resonance imaging (MRI) of the brain showing tiny foci of mild FLAIR hyperintensity at grey-white matter junction suggestive of early vasculitis changes (arrowheads).

References

1. Chen LH, Wilson ME. Dengue and chikungunya in travelers: recent updates. Curr Opin Infect Dis. 2012;25(5):523-9.
2. Singh J, Dinkar A, Singh RG, Siddiqui MS, Sinha N, Singh SK. Clinical profile of dengue fever and coinfection with chikungunya. Ci Ji Yi Xue Za Zhi. 2018;30(3):158-164
3. Bernal C, Acosta Colmán I, Cardozo F, Waggoner JJ, Cantero C, Acosta ME, et al. Delayed Diagnosis of Dengue in a Patient With Systemic Lupus Erythematosus. J Clin Rheumatol. 2020 Jun 10.
4. Betancur JF, Navarro EP, Bravo Bonilla JH, Cortés AD, Vélez JD, Echeverry A, Suso JP, Cañas CA, Tobón GJ. Catastrophic Antiphospholipid Syndrome Triggered by Fulminant Chikungunya Infection in a Patient With Systemic Lupus Erythematosus. Arthritis Rheumatol. 2016;68(4):1044.
5. Rajadhyaksha A, Mehra S. Dengue fever evolving into systemic lupus erythematosus and lupus nephritis: a case report. Lupus. 2012;21(9):999-1002
6. Talib Sh, Bhattu S, Bhattu R, Deshpande S, Dahiphale D. Dengue fever triggering systemic lupus erythematosus and lupus nephritis: a case report. Int Med Case Rep J. 2013;6:71-75.
7. Verdolin LD, Borner AR, Mussi H, Gismondi RA, Schau B, Ramos RC. [Rhabdomyolysis associated with dengue fever in a lupic patient]. Rev Bras Reumatol, 2014; 54(4): 318-21.
8. Zainal N, Tan KK, Johari J, Hussein H, Wan Musa WR, Hassan J, et al. Sera of patients with systemic lupus erythematosus cross-neutralizes dengue viruses. Microbiol Immunol. 2018;62(10):659-672.
9. Lin CF, Wan SW, Cheng HJ, Lei HY, Lin YS. Autoimmune pathogenesis in dengue virus infection. Viral Immunol. 2006 Summer;19(2):127-32
10. Green S, Rothman A. Immunopathological mechanisms in dengue and dengue hemorrhagic fever. Curr Opin Infect Dis. 2006;19(5):429-36.
11. Lam SK, Chua KB, Hooi PS, Rahimah MA, Kumari S, Tharmaratnam M, et al. Chikungunya infection--an emerging disease in Malaysia. Southeast Asian J Trop Med Public Health. 2001;32(3):447-51
12. Salam N, Mustafa S, Hafiz A, Chaudhary AA, Deeba F, Parveen S. Global prevalence and distribution of coinfection of malaria, dengue and chikungunya: a systematic review. BMC Public Health. 2018;18(1):710.
13. de Souza SP, de Moura CG. Dengue mimicking a lupus flare. J Clin Rheumatol. 2010;16(1):47-8.
14. Kamolratanakul S, Thungthong P, Nakhakes C, Kittiyanpanya C, Chonsawat P, Chamnanchanunt S. False-positive dengue IgM test result in a patient with systemic lupus erythematosus: a case report. Asian Biomed (Res Rev News) 2020; 14:209–13.
15. Harris VK, Danda D, Murali NS, Das PK, Abraham M, Cherian AM, et al. Unusual association of Kikuchi's disease and dengue virus infection evolving into systemic lupus erythematosus. J Indian Med Assoc. 2000 Jul;98(7):391-3.
16. Fontes Jardim DL, Lemos Tsukumo DM, Angerami RN, de Carvalho Filho MA, Abdala Saad MJ. Autoimmune features caused by dengue fever: a case report. Braz J Infect Dis. 2012; 16:92–95
17. Bercholc-Urinowsky IJ, Monge J, Campos-Romero HF, Reyna-Figueroa J. Chikungunya fever as a trigger for systemic lupus erythematosus? Conference: ESPID 2017 Poster. DOI: 10.13140/RG.2.2.13802.00967

18. Amaral JK, Teixeira MM, Schoen RT. Acute chikungunya fever followed by systemic lupus erythematosus. Curr Rheumatol Res 2020. 1(1): 6-8.
19. Takasaki T, Nawa M, Yamada KI, Harada M, Takeda A, Kurane I. Evaluation of dengue IgM detection tests using sera from patients with autoimmune diseases. J Virol Methods. 2002; 102:61–66.
20. Olson JK, Eagar TN, Miller SD. Functional activation of myelin-specific T cells by virus-induced molecular mimicry. J Immunol. 2002;169(5):2719-26