

## Cutaneous necrotizing vasculitis in ilheus virus infection: case report

### Vasculite cutânea necrosante na infecção pelo vírus ilheus: relato de caso

Gubio Soares Campos<sup>1</sup>, Iridan Brasileiro Costa<sup>2</sup>, Rebeca Marcelle Varjao Ferreira dos Santos<sup>3</sup>, Verônica de França Diniz Rocha<sup>4</sup>, Gilberto Tavares dos Santos Junior<sup>4</sup>, Silvia Ines Sardi<sup>1\*</sup>.

<sup>1</sup>Laboratório de Virologia, Universidade Federal da Bahia (UFBA); <sup>2</sup>Secretaria Municipal da Saúde, Camaçari, Bahia;

<sup>3</sup>Superintendência de Vigilância e Proteção a Saúde, Camaçari, Bahia; <sup>4</sup>Instituto Couto Maia, Bahia

#### Resumo

O vírus Ilhéus (ILHV) foi identificado pela primeira vez na cidade de Ilhéus, estado da Bahia, Brasil. O ILHV é um arbovírus pertencente ao gênero *Flavivirus*, família *Flaviviridae*. O ciclo enzootico entre pássaros e mosquitos mantém esse vírus na natureza, com poucos relatos de ILHV em humanos. **Objetivo:** O objetivo deste trabalho é relatar uma apresentação clínica incomum e rara de infecção pelo ILHV em humanos. **Metodologia:** Foram realizados exames de bioquímica clínica, hemograma, avaliação e acompanhamento clínico pelos profissionais de saúde atuantes e técnicas de biologia molecular, para identificar material genético de vírus nas amostras clínicas. **Resultados e Discussão:** A apresentação clínica atípica da infecção por ILHV em humano em Salvador, Bahia, Brasil é descrita, mostrando necrose dérmica associada a vasculite, perivasculite e microtrombos em membros superiores e inferiores. Os achados laboratoriais mais prevalentes foram proteína C-reativa alta, níveis elevados de enzimas hepáticas e baixo nível de plaquetas. O diagnóstico molecular detectou a presença de ILHV no soro confirmando a apresentação clínica atípica desta infecção. Este relato reforça a importância da vigilância epidemiológica de arbovírus emergentes ou reemergentes, e conscientiza os profissionais de saúde sobre as apresentações clínicas atípicas da infecção por ILHV.

**Palavras-chave:** Vírus Ilhéus; Vasculite; Necrosis cutânea; Humano; PCR

#### Abstract

The Ilhéus virus (ILHV) was identified for the first time in the city of Ilhéus, state of Bahia, Brazil. ILHV is an arbovirus belonging to the *Flavivirus* genus, family *Flaviviridae*. The enzootic cycle between birds and mosquitoes maintains this virus in nature, with few reports of ILHV in humans. **Objective:** The aim of this study is to report an unusual and rare clinical presentation of ILHV infection in humans. **Methodology:** Clinical biochemistry tests, complete blood counts, clinical evaluation and monitoring by health professionals, and molecular biology techniques were performed to identify viral genetic material in clinical samples. **Results and Discussion:** The atypical clinical presentation of ILHV infection in humans in Salvador, Bahia, Brazil is described, showing dermal necrosis associated with vasculitis, perivasculitis, and microthrombi in the upper and lower limbs. The most prevalent laboratory findings were high C-reactive protein levels, elevated liver enzyme levels, and low platelet counts. Molecular diagnosis detected the presence of ILHV in serum, confirming the atypical clinical presentation of this infection. This report reinforces the importance of epidemiological surveillance of emerging or re-emerging arboviruses and raises awareness among health professionals regarding the atypical clinical presentations of ILHV infection.

**Keywords:** Ilheus virus; Vasculitis; Skin necrosis; Human; PCR.

#### INTRODUCTION

Ilhéus virus (ILHV) was first described in 1944 during an epidemiological investigation of yellow fever in the city of Ilhéus, state of Bahia, Brazil<sup>1</sup>. ILHV, belonging to the genus *Flavivirus*, family *Flaviviridae*, is an enveloped positive-sense single-stranded RNA virus first isolated from *Psorophora* spp. and *Ochlerotatus* spp mosquitoes, and the enzootic cycle between birds and mosquitoes maintains this virus in the wild, with few reports of ILHV in humans<sup>1,2</sup>. The low level of viremia supports the theory that humans are dead-end hosts, ending the viral transmission cycle. Human infection has been sporadi-

cally reported in Trinidad<sup>3</sup>, Panama<sup>4</sup>, Colombia<sup>5</sup>, French Guyana<sup>6</sup>, Ecuador<sup>7</sup>, and Bolivia<sup>8</sup>.

The clinical spectrum of human infections ranges from asymptomatic to severe disease characterized by central nervous system involvement. Viremia lasts three to five days, and most patients exhibit a mild febrile illness accompanied by headache, myalgia, photophobia, arthralgia, skin rash, nausea, vomiting, sore throat, and abdominal pain that may suggest dengue fever, yellow fever, or influenza. Infection can potentially progress to encephalitis and/or meningoencephalitis<sup>9,10</sup>. Mild non-specific symptoms, short viremia, and a lack of routine laboratory assays are some of the barriers that may complicate an accurate ILHV diagnosis. The laboratory diagnosis of ILHV fever is based on molecular detection since the serological tests involve cross-reactivity between flaviviruses and virus isolation is time-consuming<sup>11</sup>.

**Corresponding/Correspondente:** \*Silvia Ines Sardi – Laboratório de Virologia, Instituto de Ciências da Saúde, Universidade Federal da Bahia – End: Av. Reitor Miguel Calmon s/n 40110-110 Salvador, Bahia, Brasil – E-mail: sissardi@yahoo.com.br

This report highlights a novel clinical presentation caused by the infection with ILHV. Indeed, it reinforces the need for vigilance regarding the incidence of arboviruses with unusual clinical manifestations, as demonstrated herein by the rare and atypical clinical presentation of ILHV infection in humans.

## CASE REPORT

A 41-year-old woman with hypertension, from Simões Filho City, Bahia, Brazil, was admitted at a local health unit, presenting a severe frontal headache that had lasted

for one day, associated with vomiting. She also presented a fever of 39.6 °C, dry cough, malaise, odynophagia, and adynamia. The next day, she presented petechiae and ecchymosis on her upper and lower limbs, which became hemorrhagic phlyctenae. She progressed with disorientation, mental confusion, acute respiratory failure, and syncope and required orotracheal intubation. Due to suspected meningococcal meningitis, chemotherapy was initiated with ceftriaxone 2 g 12/12h. Laboratory investigations are shown in Table 1. After six days, she was transferred to an intensive care unit.

**Table 1** – Laboratory and radiological imaging aspects in patient with suspected ILH virus infection

Laboratory Investigation	Results Reference Values
Leukocytosis	34.560 mm <sup>3</sup> 4.000 – 11.000 mm <sup>3</sup>
Platelets	88.000 mm <sup>3</sup> 150.000-450.000 mm <sup>3</sup>
Creatinine	1.98 mg/dL 0,6 a 1,2 mg/dL
Internal Normal Ratio (INR),	2.55 0.8 to 1.1.
Aspartate aminotransferase	1.027 U/L 5 – 34 U/L
Alanine aminotransferase	370 U/L 7 – 56 U/L
C-reactive protein	192 mg/dl 1 mg/dL
Culture – sepsis.	Negative
Cranial computer-aided tomography (CT) imaging	Normal
Thoracic CT imaging	Cardiomegaly, small bilateral pleural effusion, ground glass opacity, and diffuse bilateral consolidation associated with pulmonary congestion.
Cerebrospinal fluid (CSF)	Colorless
.	Two mononuclear cells 5 cell/mm <sup>3</sup>
Markers for autoimmune diseases	Glucose – 98 mg/dL 50 a 80 mg/dL
	Protein – 15 mg/dL 15 a 45 mg/dL
	Gram staining – Negative
	India ink test for <i>Cryptococcus</i> sp. – Negative
	Syphilis tests (FTA-ABS and VDRL) – Negative
	Multiplex real-time PCR assay (Filmarray) for <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i> , <i>Streptococcus pneumoniae</i> – Negative
	Gene Xpert MTB-RIF Assay G4 for <i>Mycobacterium tuberculosis</i> – Negative
	ANA (Antinuclear antibody) – Negative
	MPO-ANCA (Myeloperoxidase-antineutrophil cytoplasmic antibody) – Negative
	C3 and C4 complement tests – Negative
	Rheumatoid factor – Negative

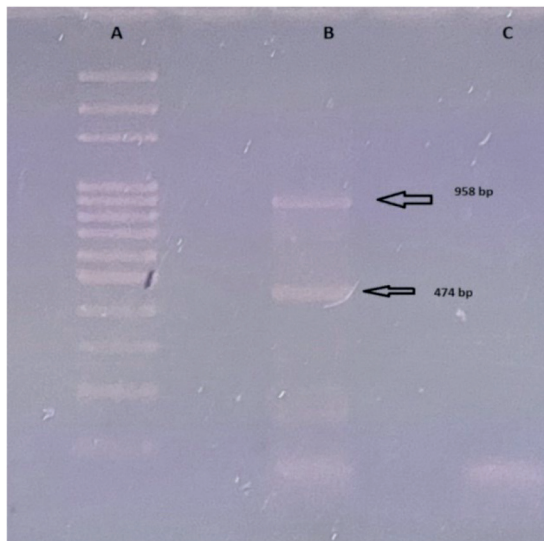
Source: research data

Blood samples were taken for viral detection by RT-qPCR of Sars-CoV-2, Respiratory Syncytial Virus, Influenza A and B (Kit Molecular INFA/INFB/SC2 Bio-Manguinhos, Brazil), with negative results. For further investigations, serum, urine, and CSF samples were taken and sent to the Laboratory of Virology (Salvador, Federal University of Bahia, Brazil). The Human Ethical Committee of Couto Maia Institute, Salvador, Bahia, Brazil approved this study (protocol number CAAE 67745223.3.0000.0046).

All samples sent to the Laboratory of Virology were subjected to arbovirus screening. The patient tested negative for Chikungunya, Dengue, Zika, Yellow Fever, and West Nile using the RT-qPCR Arbovirus Panel (SD Biosensor, Brazil). Molecular diagnoses of Oropouche and Mayaro viruses were also negative according to protocols

described by Fonseca et al.<sup>12</sup> (2020) and Waggoner et al.<sup>13</sup> (2018), respectively. The RNA extracted from serum samples was also subjected to molecular detection of the Flavivirus group according to de Moraes Bronzoni et al.<sup>14</sup> (2005). Briefly, RT-PCR was carried out initially using primers for detection of the Flavivirus group Saint Louis encephalitis virus (SLEV), Bussuquara virus (BSQV), Rocio virus (ROCV) and, ILHV. Identification via the nested-PCR of each SLEV, BSQV, ILHV, and ROCV was performed individually in different reactions, as cited by de Moraes Bronzoni et al.<sup>14</sup> (2005). The products of the nested PCR were visualized by agarose gel electrophoresis, showing only positive amplification of ILHV, represented by a 474-bp amplicon. (Figure 1). All reactions were performed using positive and negative controls.

**Figure 1** – M-N-PCR Flavivirus assay of ILHV analyzed by ethidium bromide-stained agarose gel electrophoresis (2%).



Lane A: Molecular size marker (DNA ladder, 100 bp); Lane B: Positive identification of Flavivirus group (958 bp) and ILHV (474 bp) in the patient's sample; Lane C: Negative control.

Source: own authorship

During the first month of the illness, the patient showed bilateral ecchymosis lesions on the toes and limbs (Figure 2 A). The skin ecchymosis biopsy showed dermal necrosis associated with vasculitis, perivasculitis, and microthrombi. The ecchymosis lesions on the toes progressed to necrosis without phlogistic signs, but the calcaneal arterial pulse and pediatricians indicated the need for amputation (Figure 2 B).

**Figure 2** – Skin ecchymosis in upper and lower limbs (A) and necrotic toe lesions that needed amputation (B) in the patient infected by ILHV.



Source: own authorship

Therefore, amputation of all toes was performed. Arterial and venous Doppler ultrasonography of the upper and lower extremities were normal, and no changes were detected. After the patient was in good general condition and good mental condition, she was liberated from the healthcare unit and has been stable since then.

Here, we report a case of an atypical clinical presentation of ILHV infection. Although ILHV infection usually causes mild and nonspecific symptoms, some case reports mention meningoencephalitis, intraparenchymal hemorrhage, and death<sup>10</sup>. Vasculitis is caused by an inflammatory process secondary to a viral response, with antibody deposition in blood capillaries. So far, there are no reports in the literature of an association between ILHV and vasculitis. Still, several reports of vasculitis that progressed from petechiae or purpura have been reported in cases of patients infected with Dengue virus, Lassa fever, Oropouche fever, Yellow Fever, Hepatitis C, Cytomegalovirus or HIV infections<sup>15-19</sup>.

## CONCLUSION

This case report provides evidence that contributes to the epidemiological surveillance caused by emerging or reemerging arboviruses and the importance of the awareness of health professionals about the possible atypical clinical manifestation of this arbovirus disease.

## ACKNOWLEDGMENTS

This work has been supported by the following Brazilian research agencies: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Conselho Nacional de Desenvolvimento Científico e Tecnológico, (CNPq) (Researcher Scholarship Level 1; 310866/2019-7, Silvia I. Sardi). We want to thank to Ively Santos Paixao, Silvana Oliveira Neves, Beatriz Perez Vidal for the technical support, and Evelin Moura Nascimento for medical assistance.

## REFERENCES

1. Laemmert Junior HW, Hughes TP. The virus of Ilhéus encephalitis; isolation, serological specificity and transmission. *J Immunol.* 1947;55:61-7.
2. Araújo PA, Freitas MO, Chiang JO, Silva FA, Chagas LL, Casseb SM, et al. Investigation about the Occurrence of Transmission Cycles of Arbovirus in the Tropical Forest, Amazon Region. *Viruses.* 2019;11:774. doi: 10.3390/v11090774
3. Spence I, Anderson CR, Downs WG. Isolation of Ilheus virus from human beings in Trinidad, West Indies. *Trans R Soc Trop Med Hyg.* 1962 Nov;56:504-9. doi: 10.1016/0035-9203(62)90074-3
4. Srihongse S, Johnson CM. The isolation of Ilhéus virus from man in Panamá. *Am J Trop Med Hyg.* 1967 Jul;16(4):516-8. doi: 10.4269/ajtmh.1967.16.516
5. Prias-Landínez E, Bernal-Cubides C, Morales-Alarcón A. Isolation of Ilhéus virus from man in Colombia. *Am J Trop Med Hyg.* 1968 Jan;17(1):112-4. doi: 10.4269/ajtmh.1968.17.112.

6. Panon G, Fauran P, Digoutte JP. Isolement du virus Ilheus en Guyane française Isolation of Ilheus virus in french Guyana]. *Bull Soc Pathol Exot Filiales*. 1979 Jul-Aug;72(4):315-8.
7. Johnson BW, Cruz C, Felices V, Espinoza WR, Manock SR, Guevara C, Olson JG, Kochel TJ. Ilheus virus isolate from a human, Ecuador. *Emerg Infect Dis*. 2007 Jun;13(6):956-8. doi: 10.3201/eid1306.070118
8. Venegas EA, Aguilar PV, Cruz C, Guevara C, Kochel TJ, Vargas J, et al. Ilheus virus infection in human, Bolivia. *Emerg Infect Dis*. 2012;18(3):516-8. doi: 10.3201/eid1803.111486
9. Nassar ES, Coimbra TL, Rocco IM, Pereira LE, Ferreira IB, de Souza LT, et al. Human disease caused by an arbovirus closely related to Ilheus virus: report of five cases. *Intervirology*. 1997;40(4):247-52. doi: 10.1159/000150554
10. Milhim BHGA, Estofolete CF, Rocha LCD, Liso E, Brienze VMS, Vasilakis N, et al. Fatal Outcome of Ilheus Virus in the Cerebrospinal Fluid of a Patient Diagnosed with Encephalitis. *Viruses*. 2020;12(9):957 doi: 10.3390/v12090957
11. Starolis MW, Perez O, Powell EA. Clinical features and laboratory diagnosis of emerging arthropod-transmitted viruses: A Report from the Pan American Society for Clinical Virology Clinical Practice Committee. *J Clin Virol*. 2020;132:104651. doi: 10.1016/j.jcv.2020.104651
12. Fonseca LM Dos S, Carvalho RH, Bandeira AC, Sardi SI, Campos GS. Oropouche Virus Detection in Febrile Patients' Saliva and Urine Samples in Salvador, Bahia, Brazil. *Jpn J Infect Dis*. 2020 Mar 24;73(2):164-5. doi: 10.7883/yoken.JJID.2019.296
13. Waggoner JJ, Rojas A, Mohamed-Hadley A, de Guillén YA, Pinsky BA. Real-time RT-PCR for Mayaro virus detection in plasma and urine. *J Clin Virol*. 2018;98:1-4. doi: 10.1016/j.jcv.2017.11.006
14. de Moraes Bronzoni RV, Baleotti FG, Ribeiro Nogueira RM, Nunes M, Figueiredo LTM. Duplex reverse transcription-PCR followed by nested PCR assays for detection and identification of Brazilian alphaviruses and flaviviruses. *J Clin Microbiol*. 2005;43(2):696-702. doi: 10.1128/JCM.43.2.696-702.2005
15. Costa LA da, Santos EF, Feitoza EMBA, Yamashita M, Andrade JC, Sousa PVL de. Dengue associated with severe cutaneous leukocytoclastic vasculitis and pericardial effusion: a case report. *Rev Inst Med Trop Sao Paulo*. 2020;18:62:e101. doi: 10.1590/S1678-9946202062101
16. Bothra A, Maheswari A, Singh M, Pawar M, Jodhani K. Cutaneous manifestations of viral outbreaks. *Australas J Dermatol*. 2021;62:27-36. doi: 10.1111/ajd.13421
17. Arslan F, Batirel A, Mert A, Ozer S. Cytomegalovirus (CMV)-related cutaneous necrotizing vasculitis: case report and literature review. *Braz J Infect Dis*. 2012 Sep-Oct;16(5):482-5. doi: 10.1016/j.bjid.2012.08.002
18. Alkhatib AA, Adler DG. Cutaneous necrotizing vasculitis associated with hepatitis C virus infection. *Dig Dis Sci*. 2007 Dec;52(12):3438-9. doi: 10.1007/s10620-006-9599-x
19. Ariza Ordoñez N, Sepúlveda VG, Marín AP, Vargas Nieto LP, León JM, Prada HAM. Leukocytoclastic vasculitis in a patient with syphilis and HIV coinfection. *Rev Inst Med Trop Sao Paulo*. 2022 Sep 30;64:e65. doi: 10.1590/S1678-9946202264065

---

SUBMISSÃO: 21/01/2025

ACEITE: 09/04/2025