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Lorena Martel Uruçu

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Orientadora: Dra. Ianick Souto Martins

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DEDICATÓRIA

Dedico este trabalho aos pacientes, pois me ensinaram, e ensinam, a ser cada vez mais simples, mais fraterno e mais humano.

AGRADECIMENTOS

Agradeço a sabedoria universal, mente cósmica onipresente, a que chamamos de Deus, pois é Dele que tudo flui e a que tudo retorna.

EPÍGRAFE

"Senhor que és Deus, se eu Te busco pelo medo do Teu inferno, queima-me no Teu inferno! Se eu Te busco pelo desejo do Teu céu, expulsa-me do Teu Céu. Mas se eu Te busco apenas pelo que és, recebe-me no seio da Tua glória e revela-me a Tua face."

Rabia A Adawiyya – tradição Sufi

Lethal encephalitis due to Chikungunya virus in a patient with *Myasthenia Gravis* and associated thymoma: a case report

Lorena Martel Uruçu[1], André Gustavo Neves de Albuquerque[1], Christian Naurath[2] Marcia Carreira[3], Marianne Monteiro Garrido[4], Vanessa E. Emmel[5], Bianca E. Gamma[5], Rocio Hassan[5], Ianick Souto Martins[4].

[1]Intensive Care Unit, [2]Neurology Section, [3]Pneumology Section, [4]Infection Control Section, of Hospital do Cancer I, Instituto Nacional do Cancer (INCA), Rio de Janeiro, Brazil

[5]Oncovirology Laboratory, Bone Marrow Transplantation Center (CEMO), INCA

Corresponding author: Lorena Martel Uruçu

Address: Hospital do Câncer I, Praça da Cruz Vermelha, 23, Centro, Rio de Janeiro, Brazil. Zip code: 20230-130. Phone: 55 21 99837-2075.

E-mail: lorena_martel@hotmail.com

INTRODUCTION

Chikungunya virus (CHIKV) is a reemerging arbovirus transmitted, in most cases, by the bite of female mosquitoes of *Aedes* genus (*aegypti* and *albopictus*).(1) CHIKV is an RNA virus belonging to the *Togaviridae* family, genus *Alphavirus*.(2)

In Brazil, autochthonous cases of CHIKV fever were firstly reported in 2014. These cases were detected in Amapá and Bahia States (North and Northeast of Brazil). Thereafter, the disease was reported in all states of the country and epidemics were declared in some states of the Northeast and Southeast. Nowadays, the intense movement of people in areas with transmission of the virus associated with the high density of *Aedes* along the country and the presence of susceptible individuals make epidemics a possible threaten for all regions of the country.(2)

In 2018, among 81.597 probable cases of Chikungunya reported in Brazil, the Southeast had the highest number of cases (52,966 cases; 60.4%), followed by the Midwest (13 862 cases; 15.8%), Northeast (11,287 cases; 12.9%), North (9,315 cases; 10.6%) and South (257 cases, 0.3%). In the latest epidemiological report, 39 deaths by laboratory confirmed CHIKV infection were reported, while 42 deaths are still under investigation.(3)The clinical presentation of CHIKV infection is similar to that of other arboviruses such as Dengue (DENV) and Zika virus (ZIKV) infections. The disease usually begins with high fever, arthralgia, myalgia, headache, nausea, fatigue and skin rash. Intense arthralgia is the major clinical manifestation, which can often be accompanied by joint swelling.(4)·(5) Rarely, severe illnesses with complications such as myocarditis, hepatitis, Guillain-Barré syndrome (GBS), encephalitis and meningoencephalitis were reported.(6) Infection of the central nervous system (CNS) by

CHIKV can present a wide spectrum of signs and symptoms. The disease can be severe with unfavorable outcome due to the virus tropism for the CNS.(1)

The potential association between the presence of immunosuppressive conditions and more serious disease caused by CHIKV, such as encephalitis, are widely unknown. In the present study, we report a case of a lethal encephalitis caused by CHIKV infection in a patient *with immunosuppressive therapy for Myasthenia Gravis* and associated thymoma. The patient was diagnosed with viral infection at the Instituto Nacional do Câncer Hospital I (INCA-HCI), Rio de Janeiro, Brazil in 2018. CHIKV infection was confirmed by polymerase chain reaction (PCR) in a reference laboratory at INCA. The study was approved by the Research Ethics Committee of the Instituto Nacional do Câncer (CAAE 60385416.1.0000.5274).

METHODS

Epidemiological and clinical data were collected through examination of the patient at the bedside and review of medical records. Differential diagnosis among CHIKV, DENV and ZIKV was performed by standarized retrotranscription (RT) mediated quantitative PCR (RT-qPCR) recommended by Centers for Disease Control and prevention/ CDC (USA) and Pan American Health Organization/PAHO (7,8) from viral RNA extracted from samples of cerebrospinal fluid, blood serum and urine. Herpesvirus infections (HSV-1 to HHV-8), adenovirus, BK and JC polyomavirus, B19 parvovirus and *Toxoplasma gondii* infections were evaluated by PCR assays with specific primers in DNA extracted from the CNS fluid.

CASE-REPORT

Female patient, 45 years, with *Myasthenia Gravis* in specific therapy with prednisone and azathioprine. She had been diagnosed with thymoma in 2009, which was treated with surgical resection, chemotherapy and radiotherapy.

On 04/06/2018 (Day1), fever appeared as first symptom, followed by skin rash and polyarthralgia of large joints. On 04/10/2018 (Day 4), the patient developed headache and lethargy. On 04/13/2018 (Day 7), she was admitted to INCA-HC1 due to progressive worsening of the general condition, headache and arthralgia without response to analgesia. Physical examination revealed skin rash with petechiae in the trunk and limbs with greater concentration on the edge of the upper limbs, subconjunctival petechiae, and edema in wrist and knee joints mainly; abnormal consciousness (lethargic but responsive to verbal commands), with voluntary movement of arms and legs capable of overcoming "some" resistance, no focal findings or signs of meningeal irritation. Initial white blood cell count (WBC) of 13630; 82% neutrophils, 9.6% lymphocytes and 279,000 platelets/mm^3, which ensued with subsequent progressive decrease of platelet counts. Clinical hypotheses were infectious syndrome and decompensation of *Myasthenia Gravis*. Laboratory and image exams consisted of blood and cerebrospinal fluid (CSF) cultures; measures of CSF glucose, protein and cellularity; Computed Tomography (CT) scan of the cranium; Trans-thoracic echocardiography (TTE); and finally viruses as described in Methods to research for rash viruses, encephalitis, sepsis and infective endocarditis (IE). Empiric treatment was initiated with immunoglobulin and piperacilin-tazobactam.

On 04/17/2018 (Day 11), the patient developed respiratory failure and neurological deterioration (deep stupor) with brainstem reflexes present and, having

been transferred to the Intensive Care Unit (ICU). The CSF analysis (04/17/2018) showed presence of pleocytosis with lymphocytic predominance (cellularity 118 cells/mm^3, lymphocytes117 cells/mm^3) with mild elevation of protein and decrease of glucose concentrations (Protein 143 mg/dL, glucose 70 mg/dL), findings suggestive of viral meningoencephalitis. Significant changes were not observed in the first CT (04/18/2018), while in the second CT, 24 hours later brain edema was evident (Figure 1). The TTE (04/18/2018) showed no findings suggestive of IE. At this time (04/17/2018), the antibiotic therapy was changed for ceftriaxone, vancomycin and acyclovir. Blood cultures and CSF cultures showed no growth of microorganisms. RT-qPCR was positive for CHIKV in CSF, serum and urine (04/18/2018), while negative for all other investigated pathogens. CHIKV viral loads were estimated by reverse calibration on a standard curve and were 61,711,049.75 copies/mL in serum; 27,305.74 copies/mL in urine and 300,861.75 copies/mL in the CSF (Figure S1).

Between 04/17/2018 (Day 11) and 04/19/2018 (Day 13), neurological findings revealed progressive brain activity deterioration with coma, pupils with median dilation and without light reaction, bilateral reduction of corneal blink reflex response, oculocephalic response present in the right side only, cessation of the cough reflex and presence of respiratory drive. In 05/02/2018 (Day 26), despite the life support measures administered in the ICU, the patient developed clinical evidence of irreversible brain failure with dilated pupils, cessation of brainstem reflexes, refractory shock, and finally died.

DISCUSSION AND CONCLUSION

In the present study, a rare and fatal case of meningoencephalitis caused by CHIKV infection was reported in a patient undergoing immunosuppressive therapy for

Myasthenia gravis and associated thymoma. This is the fifth case reported in the world and the first to be described in an immunocompromised patient. Infection of CNS caused by CHIKV infection was first reported during an outbreak in 1964, in Madras, India.(9) Since then, four reported cases were confirmed by serology or viral isolation. Of these, two had meningoencephalitis; one had acute flaccid paralysis and high CSF protein, suggestive of GBS; and transient dysarthria. Since then, neurological manifestations have been reported across the Indian Ocean, South Asia, the Pacific Islands, southern Europe, the Caribbean and South America, ranging from mild behavioral disorders, to severe acute syndromes of the CNS and the peripheral nervous system.(6)

CHIKV infection can affect many systems, including central and peripheral nervous system.(10),(11) In two studies investigating manifestations in patients who required intensive care, neurological disorders were the main problem in 61% and 79% of cases.(12),(13) Among 99 cases of neurological disease associated with CHIKV infection described in India, 69 also had other complications involving, for example, renal, hepatic and respiratory systems.(14)

Encephalopathy is one of the most common neurological presentations in arbovirus infection.(15) Although in some patients, encephalopathy is due to encephalitis, in others it may be a non-specific manifestation of a severe systemic disease only, for example due to cerebral hypoperfusion.(16),(17) Strictly speaking, encephalitis is a pathological diagnosis, but for practical purposes, it can be diagnosed in a patient with encephalopathy if there is evidence of brain inflammation. In the present study, the inflammatory characteristics of CSF, the detection of CHIKV in CSF by PCR, and the CT showing brain edema support the encephalopathy followed by brain death was due to meningoencephalitis caused by CHIKV.(18),(16)

At present, there are limited data on the association of CHIKV severe manifestations in patients with comorbidities and immunosuppression. Some descriptions of correlations between severe manifestations and arboviruses co-infection have been described, which does not correspond to the herein described case.(19),(20) In the present study, we report on a immunocompromised patients due to underlying immunological disease and treatment with immunosuppressive drugs, who evolved with encephalitis after CHIKV infection. This case add significant data to the limited literature on the subject and raise further studies to corroborate this correlation, in order to identify risk groups for severe manifestations.

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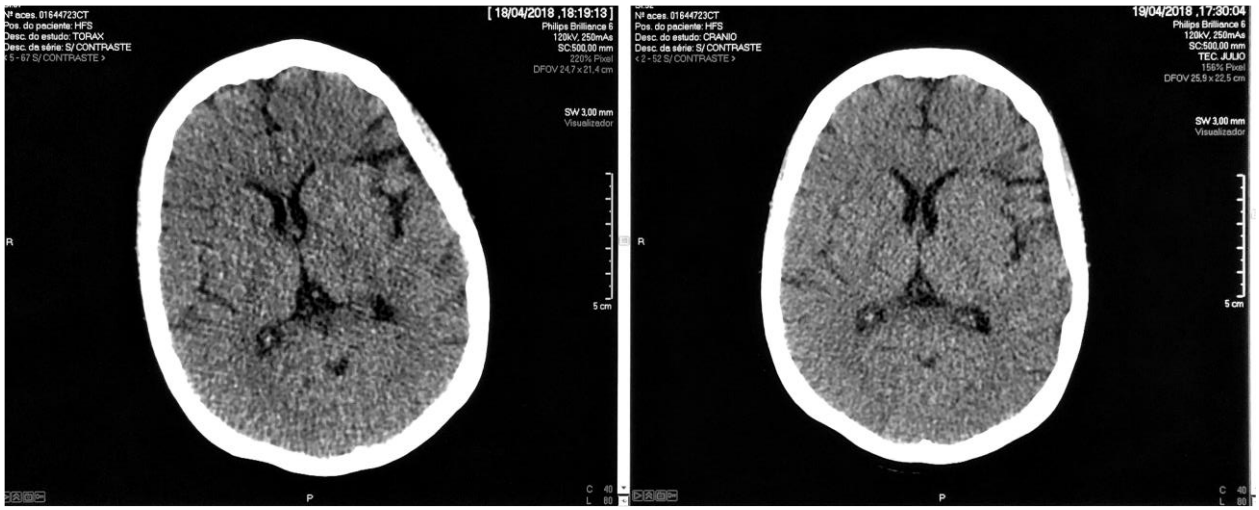
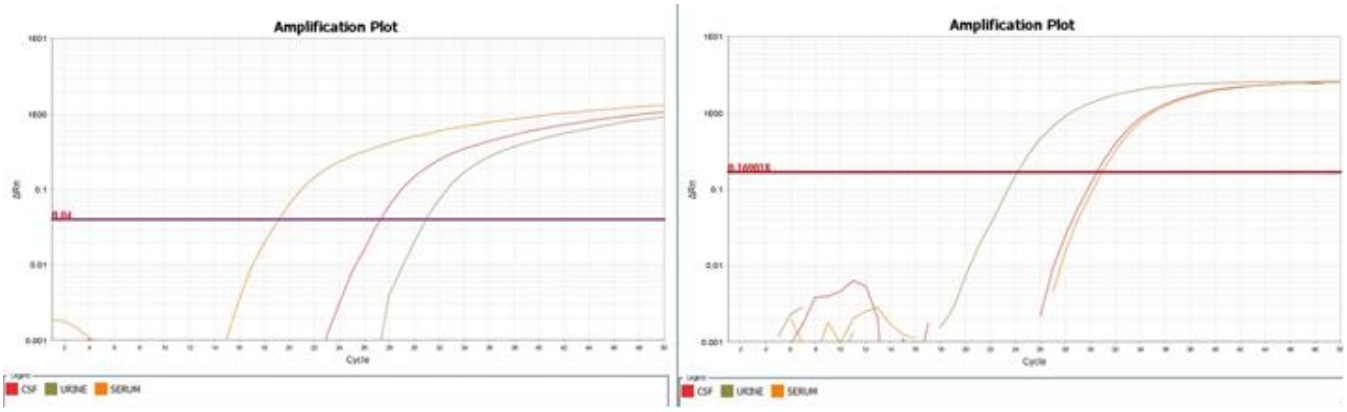
LEGENDS

FIGURE 1



Note. Computed tomography scan of cranium, on 04/18/2018 (image in the left side) and 04/19/2018 (image in the right side), showing the development of evidence brain edema along the period of 24 hours.

FIGURE S1



Note. Amplifications plots for A: CHIKV; B: b-2 microglobulin (constitutive gene) amplifications, in serum, urine and CSF samples from the case. Total RNA was extracted from 140 µl of samples using QIAamp® Viral RNA kit (Qiagen). After

complementary DNA synthesis (cDNA) using Superscript™ II Reverse Transcriptase (Invitrogen, Thermo Fisher Scientific), the cDNA was subjected to qPCR using specific CHIKV primers and fluorescent probe (Lanciotti et al. 2007). Reactions were run on a Viia7 Real-time PCR System (Applied Biosystems, Thermo Fisher Scientific). Each run included b-2 microglobulin amplification (B) used as internal control to check for a suitable RNA extraction and cDNA synthesis. A positive diagnosis was performed by analyzing Ct, when a specific sample exhibited a Ct value < 38 cycles. Quantification was performed in a separate run by reverse calibration onto a standard curve made over a 6-log of 10-fold serial dilutions of synthetic oligo DNA template (IDT) in an enriched yeast-tRNA (Ambion, 100ng/□L) Tris-EDTA buffer (not shown).