Rev Soc Bras Med Trop 49(5):648-652, September-October, 2016
doi:10.1590/0037-8682-0093-2016

Case Report

Mayaro fever in an HIV-infected patient suspected of having Chikungunya fever

***Cássia Fernanda Estofolete*[1], *Mânlio Tasso Oliveira Mota*[1], *Danila Vedovello*[1], *Delzi Vinha Nunes de Góngora*[1], *Irineu Luiz Maia*[1] *and Maurício Lacerda Nogueira*[1]**

[1]. Departamento de Doenças Dermatológicas, Infecciosas e Parasitárias, Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, São Paulo, Brasil.

Abstract

Arboviruses impose a serious threat to public health services. We report a case of a patient returning from a work trip to the Amazon basin with myalgia, arthralgia, fever, and headache. During this travel, the patient visited riverside communities. Both dengue and Chikungunya fevers were first suspected, tested for, and excluded. Mayaro fever was then confirmed by reverse transcription polymerase chain reaction followed by next-generation sequencing and phylogenetic reconstruction. The increased awareness of physicians and consequent detection of Mayaro virus in this case was only possible due a previous surveillance program with specific health personnel training about these neglected arboviruses.

Keywords: Mayaro. Chikungunya. HIV.

INTRODUCTION

Arboviruses are a diverse set of viruses grouped together by their complex life cycles, which involve arthropod-based transmission to vertebrate hosts. They pose a major threat to public health in many tropical countries[1]. In the tropical Americas, the most important arboviruses are dengue virus (DENV) and yellow fever virus (YFV)[1]. However, other neglected, emerging, or re-emerging arboviruses, such as those belonging to the families *Togaviridae* or *Bunyaviridae*, are also important[1]. Mayaro virus (MAYV) belongs to the arthritogenic group of alphaviruses along with Chikungunya virus (CHIKV); they cause a dengue-like febrile syndrome with arthralgia/arthritis. MAYV is the main arthritogenic virus in South America. CHIKV is predominant in Africa but has spread to Asia, Pacific Oceanic countries and, recently, to South America. MAYV causes a mild to severe illness characterized by fever, headache, rash, malaise, myalgia, large joint arthralgia and, sometimes, arthritis, similar to that caused by CHIKV. Although MAYV does not cause hemorrhagic fever, it can be very debilitating due to the arthritis that can persist for months[2].

Since the first description of autochthonous cases of Chikungunya fever in the Americas in November 2013[3], Brazil's Ministry of Health compiled a national contingency plan, aiming to establish appropriate strategies to prevent the import and spread of the virus and to guide clinical management of the disease[4]. The first outbreak of Mayaro fever in Brazil was reported in 1957, in Para State, affecting about 100 individuals[5]; MAYV was isolated from six patients. Since then, there has been no standardized federal system for surveillance of this arbovirus. There are few studies on the true incidence of MAYV, detected mostly in the Amazon region and Central Highlands[5] (**Figure 1**). Many countries in these areas also face serious public health problems because of the acquired immunodeficiency syndrome (AIDS) epidemic, but the possible role of immunosuppression in the outcome of arbovirus infections is unclear[6].

We report here the case of an HIV-infected patient who returned from a work trip to the Amazon basin and was admitted at the infectious diseases service of the Hospital de Base (HB) of the Medical School of São José do Rio Preto, São Paulo State, Brazil. Both DENV and CHIKV were tested for and excluded. Based on clinical and epidemiological data, MAYV was suspected and subsequently confirmed by reverse transcription -polymerase chain reaction (RT-PCR) testing, followed by next-generation sequencing and phylogenetic reconstruction.

CASE REPORT

A 27-year-old, human immunodeficiency virus (HIV)-infected man was admitted to the HB infectious diseases service with a 10-day history of myalgia, arthralgia, fever (38-40ºC), and holocranial headache. There were no cutaneous rashes or other skin manifestations. The patient denied the use of alcohol,

Corresponding author: Dr. Maurício Lacerda Nogueira.
e-mail: mnogueira@famerp.br
Received 18 March 2016
Accepted 23 June 2016

FIGURE 1. Circulation of Mayaro virus in Brazil. The map shows the locations of reports of MAYV, indicating the virus circulation. It indicates reports of virus isolation from human samples (human figure) or from culicids (insect figure) and also serological evidence from human, animal, or vector samples (antibody figure). The human figure with asterisk is the case described in this work. **MAYV:** Mayaro virus.

tobacco, or injectable drugs. He reported having been on a work trip to the City of Portal in the interior of Pará State 40 days prior to admission. During this travel, he visited different populations, including riverside communities.

The early biochemical laboratory results were within normal limits (C-reactive protein: 0.61mg/dL; alanine aminotransferase (ALT): 30U/L; aspartate aminotransferase (AST): 17U/L; gamma glutamyl transferase (GGT): 17U/L; total bilirubin: 0.38mg/dL; unconjugated bilirubin: 0.2mg/dL; conjugated bilirubin: 0.18mg/dL; alkaline phosphatase: 38U/L; creatinine: 0.9mg/dL; amylase: 40U/L; prothrombin activity: 91%; international normalized ratio (INR): 1.06; hemoglobin: 12.8g/dL). He had a reactive serological test for HIV, a T $CD4^+$ cell count of 306 cells/mm^3, and viral load of 21,351 copies/mm^3. The VDRL test result was positive (titer 1:8); the patient was unaware of this. Natural immunization against

hepatitis B was detected. Serological tests (IgM) for yellow fever were inconclusive, probably due to a vaccination burst 37 days before the start of the symptoms. A thick blood smear for malaria was also negative.

Both DENV and CHIKV were ruled out by serological testing (IgM) and RT-PCR in a public health reference laboratory. Both viruses were also tested for by RT-PCR in our laboratory; the results were negative. An MAYV RT-PCR test, developed by our laboratory for the E1 gene, was performed and the result was confirmed as positive.

Viral isolation was performed in C6/36 cell culture, and MAYV was confirmed by another RT-PCR test. The virus was directly sequenced from the patient serum using Next Generation Sequencing in an Ilumina Platform (Illumina, San Diego, CA, USA). The genome was submitted to GenBank, named MAYV BR/SJRP/01/2014 (accession number: KT818520.1)[7]. Phylogenetic reconstruction was performed with MEGA v.6.0 (**Figure 2**). The MAYV BR/SJRP/01/2014 was grouped within the L clade, found only in the Pará State, supporting the epidemiological profile of the patient.

According to the recommended clinical protocol and therapeutic guidelines for the management of an HIV-infected patient with a $CD4^+$ count <350 cell/mm^3 and reactive serum VDRL, a lumbar puncture was performed. The cerebrospinal fluid (CSF) showed a slight increase in protein, a discrete lymphomonocytic pleocytosis, and a reactive CSF-VDRL test (titer 1:2). The patient was hospitalized for treatment of asymptomatic neurosyphilis; he received parenteral penicillin for 10 days. The patient experienced spontaneous relief of the myalgia and arthralgia, and was discharged with no symptoms. He remains under outpatient follow-up.

Ethicals considerations

The patient's serum was collected and tested in an arbovirus surveillance program (Ethical Review Board # 2078812.8.00005414).

DISCUSSION

Mayaro fever is a neglected disease due to two factors: inadequate surveillance in endemic areas and the generic nature of clinical manifestations that results in misdiagnosis with other viral fevers, mainly DENV[5]. Viral fevers are endemic in low socioeconomic areas and, subsequently, smaller investments are made in research, surveillance, and investigation of epidemics; many studies on arboviruses merely describe cases. Furthermore, this virus causes a dengue-like febrile syndrome with arthralgia/arthritis and the diagnosis relies only on clinical manifestations[7]: what seems like dengue must be dengue. Diagnosis based only on clinical findings may lead to misdiagnosis of MAYV as DENV or other viruses, resulting in underestimation of MAYV infections. Because there is no standard method to detect MAYV, little investment is made in MAYV research, and awareness remains low, creating a vicious cycle.

Despite outbreaks in large cities, MAYV fever is generally regarded as being limited to forests and rural areas[5]. Usually the patients are rural workers who use the forest for subsistence or live in its proximity[1]. In the urban centers, physicians attending potential MAYV-infected patients do not even consider MAYV. Many patients harboring the virus may be misdiagnosed due to the lack of laboratory tests. The high mobility of the population and the potential of MAYV to be propagated to urban *Aedes spp*. mosquitoes highlights its urbanization potential, similar to CHIKV. CHIKV, a related arthritogenic alphavirus, was originally limited to Africa but rapidly spread to Asian and Pacific Oceanic countries, causing explosive outbreaks and overburdening their health systems[8].

The emergency of CHIKV in South America, specifically in Brazil, prompted the public health authority to start a surveillance program with specific health personnel training about this arbovirus[4]. This strategy included systematic surveillance for acute febrile illnesses and an efficient laboratory diagnosis for arbovirus. This resulted in the discovery of this case, that would probably have been ignored had it occurred in any other region, simultaneously with large dengue outbreaks, or in the absence of an arbovirus surveillance system or laboratory diagnostic methods. Only three other cases have been reported in patients in São Paulo State, imported from Mato Grosso do Sul[9], making us believe that many cases are misdiagnosed.

HIV is another major public health problem; it is highly prevalent in many arbovirus-endemic regions. Due to increased mobility of the population, may we see an increase in imported cases of MAYV and other arboviruses in urban areas. HIV-infected patients may be more vulnerable to these infections, with an unpredictable outcome. Both arbovirus and HIV infections change the host's immunological response. The interplay between these two infections is poorly understood. Theoretically, the immunosuppression caused by HIV can interfere with the severity of some infections, leading to more aggressive and atypical manifestations[10]. However, the influence of these infections on the outcome of HIV infection is not well determined[11]. DENV infection causes a transient reduction in HIV load, apparently without impact on the clinical outcome of dengue fever or AIDS[12]. However, there is no information about the interaction of HIV with other arboviruses. In this case, the virus was isolated after 10 days of the febrile illness. Since MAYV viremia is usually limited to 3-7 days[5], this indicates an extended viremia, which may have been due to the patient's immunocompromised state. The relief of myalgia and arthralgia, without the need for corticoids or analgesics, indicates spontaneous clearance of MAYV infection, despite a prolonged viremia, suggesting that HIV did not affect the outcome of Mayaro fever.

As no vaccine or specific treatment is available, vector control is the most effective action to limit the spread of arboviruses. Effective health policies are only achievable if based on correct epidemiological data. This case report highlights the urgent need for more effective and broader laboratory surveillance in endemic areas in South America, specifically in Brazil. Training of health personnel increases awareness about neglected viruses, and makes physicians more attentive to patients at higher risk, such as travelers returning from endemic areas. This can improve the diagnostic accuracy of arbovirus infections and, consequently, can improve public health policies.

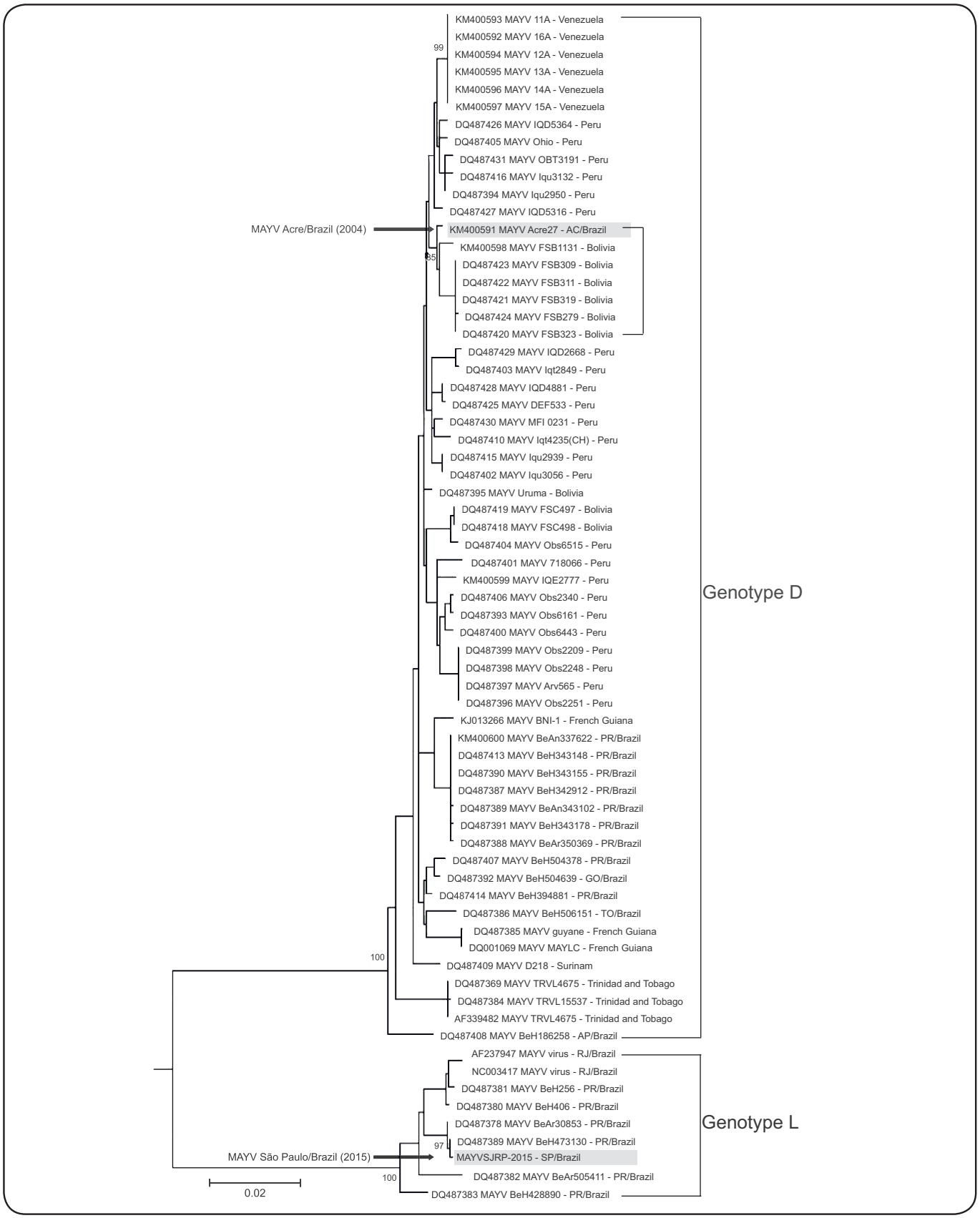

FIGURE 2. Phylogenetic tree of some MAYV sequences. Maximum likelihood phylogenetic tree of 68 sequences of MAYV based on 1,740pb of partial envelope protein (E1 and E2). The phylogenetic tree was inferred by maximum likelihood, using the Tamura-Nei model as nucleotide substitution model (MEGA 6 - www.megasoftware.net). The "L" and "D" genotypes are shown in the tree. The sample from the patient is displayed in grey. The strains are identified by the GenBank accession number, the name of the strain and country isolation. For all Brazilian strains the state the virus was isolated from is also indicated: AC: Acre; AP: Amapá; GO: Goiás; PR: Pará; RJ: Rio de Janeiro; SP: São Paulo; TO: Tocantins. The scale bar represents 0.02 nucleotide substitutions/per site/per year. The bootstrap was calculated with 1,000 replicates and values (in percentage) are shown in the main nodes of the tree. Only the values of the main nodes are shown. **MAYV:** Mayaro virus.

Conflict of Interest

The authors declare that there is no conflict of interest.

Financial Support

This work was supported by the São Paulo Research Foundation [grants # 2013/21719-3 and 2014/05600-9]. Nogueira, ML is a recipient of a CNPq PQ Fellowship.

REFERENCES

1. Weaver SC, Reisen WK. Present and future arboviral threats. Antiviral Res 2010; 85:328-345.
2. Santiago FW, Halsey ES, Siles C, Vilcarromero S, Guevara C, Silvas JA, et al. long-term arthralgia after Mayaro virus infection correlates with sustained pro-inflammatory cytokine response. PLoS Negl Trop Dis 2015; 9:e0004104. doi: 10.1371/journal.pntd.0004104.
3. Pan American Health Organization (PAHO). Chikungunya (Internet), Washington 2014. Updated 30 June 2014; cited 2015 30 Setember 2015. Available from: http://www.paho.org/hq/index.php?option=com_content&view=article&id=8303&Itemid=40023&lang=en
4. Ministério da Saúde. Secretaria de Viglância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Plano de Contingência Nacional para a Febre de Chikungunya. Brasília: Ministério da Saúde; 2014. p. 48.
5. Mota MTO, Ribeiro MR, Vedovello D, Nogueira ML. Mayaro virus: a neglected arbovirus of the Americas. Future Virol 2015; 10:1109-1122.
6. Simon V, Ho DD, Abdool Karim Q. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. Lancet 2006; 368:489-504.
7. Mota MTO, Vedovello D, Estofolete C, Malossi CD, Araujo Jr JP, Nogueira ML. Complete genome sequence of Mayaro virus imported from the Amazon basin to São Paulo State, Brazil. Genome Announc 2015; 3:e-01341-15. doi: 10.1128/genomeA.01341-15.
8. Long KC, Ziegler SA, Thangamani S, Hausser NL, Kochel TJ, Higgs S, et al. Experimental transmission of Mayaro virus by *Aedes aegypti*. Am J Trop Med Hyg 2011; 85:750-757.
9. Coimbra TLM, Santos CLS, Suzuki A, Petrella SMC, Bisordi I, Nagamori AH, et al. Mayaro virus: imported cases of human infection in São Paulo State, Brazil. Rev Inst Med Trop São Paulo 2007; 49:221-224.
10. Karp CL, Neva FA. Tropical infectious diseases in human immunodeficiency virus-infected patients. Clin Infect Dis 1999; 28:947-963.
11. Karp CL, Auwaerter PG. Coinfection with HIV and tropical infectious diseases. II. Helminthic, fungal, bacterial, and viral pathogens. Clin Infect Dis. 2007; 45:1214-1220.
12. Pang J, Thein TL, Lye DC, Leo YS. Differential clinical outcome of dengue infection among patients with and without HIV infection: a matched case-control study. Am J Trop Med Hyg. 2015; 92: 1156-1162.