Case Report

First description of a clinical case of murine typhus in Campeche, Mexico

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Abstract
Murine typhus is a flea-borne disease caused by Rickettsia typhi, which was first detected in Mexico in 1927. It was not until 1996 that the first systematized study involving this pathogen was conducted in two coastal states of Mexico. We now report the first confirmed case of murine typhus in the state of Campeche, which occurred in a male patient who exhibited fever, thrombocytopenia, hyperbilirubinemia, and a rash. Furthermore, the patient reported having had previous contact with Rickettsia reservoirs.

Keywords: Rickettsia typhi. Murine typhus. Ectoparasites.

INTRODUCTION
The genus Rickettsia comprises 33 species, which are transmitted to vertebrates by hematophagous arthropods such as ticks, mites, sucking lice, and fleas1. In vertebrate hosts, rickettsiae invade the endothelial cells of small blood vessels causing increased vascular permeability and edema, which can be fatal. Two members of the typhus group (Rickettsia prowazekii and Rickettsia typhi) have caused diseases worldwide. In Mexico, murine typhus caused by R. typhi and transmitted mainly by the rat flea (Xenopsylla cheopis)2 was first reported in 1927. However, it was not until 1996 that a systematized study of rickettsioses was carried out, recording the first cases in Yucatan and Jalisco. Although several cases of murine typhus have recently been reported in Yucatan, only a few reports have been made in other southeastern states of the country. Particularly in Campeche, only a few unpublished and incomplete records exist of R. typhi, which lack clinical descriptions of patients.

We now report the first confirmed case of murine typhus in Campeche, including clinical data of the patient and epidemiological factors of exposure to Rickettsia reservoirs.

CASE REPORT
A 34-year-old male patient from the municipality of Tenabo, Campeche, with no history of chronic diseases, was attended by a physician in June 2017 due to general malaise, fever, myalgia, arthralgia, asthenia, adynamia, and hyporexia. The patient, a journalist, was treated with antipyretics and ciprofloxacin, and showed partial improvement. Due to the persistence of his signs and symptoms, laboratory studies were undertaken. Of note, the febrile reaction to Proteus OX-19 was 1:80, and dengue IgM and IgG assay results were negative. Laboratory tests for other febrile diseases yielded negative results as well. Marked thrombocytopenia was detected (platelet count, 32,000/µL) and the patient was referred to a specialty hospital on July 3, two weeks after the onset of the symptoms. By then, the patient complained of pain in the epigastrium, dyspnea, generalized pruritus, and received the antibiotics ceftriaxone...
and doxycycline. The pain in the epigastrium, splenomegaly, generalized rash, petechiae, and intermittent fever continued throughout the second day of hospitalization. Leptospirosis was suspected and blood and urine samples were sent to the Biomedical Research Center for the detection of *Leptospira* by darkfield microscopy and polymerase chain reaction (PCR) assay of the blood and urine. Blood tests showed elevated levels of direct bilirubin (1.2 mg/dL), total bilirubin (1.9 mg/dL), alanine aminotransferase (84 U/L), gamma-glutamyltransferase (317 U/L) and alkaline phosphatase (371 U/L). However, the serum concentration of albumin (3.3 g/dL) and sodium (132 mmol/L) were decreased, as was the platelet count (21,000/µL). Other blood parameters were normal and tests for the diagnosis of leptospirosis showed negative findings.

After 4 days of treatment, the patient was hemodynamically stable, hydrated, neurologically integrated, with an adequate respiratory pattern and good clinical evolution. The patient was discharged and managed by external consultation.

Since the leptospirosis test results were negative, and the patient reported having rats in his home and having a ferret as a pet, rickettsiosis was suspected. Tests of febrile antigens were repeated and showed an elevated titer of 1:1280 for Proteus OX-19. On the second day of hospitalization, a blood sample was obtained to isolate DNA that was sent to the Experimental Medicine Unit of the National Autonomous University of Mexico and a PCR test for *Rickettsia* was done. DNA extraction was carried out from the whole blood sample using a DNeasy Blood & Tissue kit (Qiagen, Hilden, Germany). To verify the integrity of the DNA, an amplification of a 400 bp fragment of the mitochondrial gene cytochrome oxidase subunit I was performed. PCR was performed using the primers proposed by Roux and Raoult4 that amplify an 800 bp fragment of the *sca* gene that is exclusive to the genus *Rickettsia*. The PCR product was sequenced and the electropherograms were analyzed by means of the Chromas program and the sequence was compared with those of references deposited in GenBank using the BLASTn tool. The sequence was identical to the *Rickettsia typhi* strain Wilmington (GenBank accession number AE017197.1).

An indirect immunofluorescence serology test was also performed, showing *Rickettsia typhi* IgM and IgG titers of 1:256 (both), likewise *Rickettsia rickettsii* IgM and IgG titers of 1:32 and 1:64, respectively.

**Ethical considerations**

The authors declare that no experiments have been conducted on humans or animals for this research.

**Confidentiality of the data**

The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent**

The authors have obtained the informed consent of the patient referred to in this article. This document is in the possession of the corresponding author. The authors declare that the name of the patient does not appear in this article.

**DISCUSSION**

The clinical picture of rickettsial diseases is nonspecific, with fever, headache, nausea, vomiting, myalgia, malaise, arthralgia, and abdominal pain5. Likewise, various alterations of laboratory tests, mainly thrombocytopenia, azotemia, and prolongation of coagulation times are also frequent6–8.

The patient described in this study presented a prodromal phase similar to other illnesses, including the presence of thrombocytopenia and hyperbilirubinemia, likewise abnormal values of liver enzymes indicating mild hepatic damage. Due to the initial suspicion of leptospirosis, he was treated with ceftriaxone and doxycycline, and since doxycycline is also recommended for the treatment of rickettsial infections9, the patient began to recover by the fourth day of treatment. In this case, the combined empirical use of the antibiotics during the therapy had the purpose of ensuring the clinical improvement of the patient.

A presumptive diagnosis of rickettsiosis was established once the leptospirosis tests were returned negative and a second test result for Proteus OX-19 was positive, together with a history of exposure to risk factors for *Rickettsia* infection. Although the Proteus OX-19 test has a low sensitivity, it can be used as a screening test for a presumptive diagnosis. The initial diagnostic reference test for rickettsiosis is based on serology, detecting anti-*Rickettsia* antibodies by indirect immunofluorescence. Yet, the combination of the serologic test with PCR analysis, allows for further identification of the *Rickettsia* strains. It is also of paramount importance to consider the epidemiological history of the patient, since it enables the physician to detect risk factors for the infection with a given pathogen, likewise to be considered that the cat flea can play an important role in the transmission of *Rickettsia* to humans. In the present case, the nonspecific signs of the clinical picture taken together with not having considered risk factors for *Rickettsia* infections led to an erroneous initial suspicion of leptospirosis, which resulted in a late diagnosis of rickettsiosis.

In conclusion, patients with a prolonged febrile illness call for careful evaluation of both clinical and epidemiological antecedents. Rickettsiosis must be considered, once other pathogens, causing nonspecific febrile symptoms, have been ruled out.

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**Conflict of interest**

The authors declare no conflict of interest for the publication of this manuscript.

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