

Artículo Original

Enmascaramiento de tifo murino durante un brote epidemiológico de dengue en Yucatán, México. Reporte de un caso

Murine typhus masking during a dengue outbreak in Yucatán, Mexico: A case report

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RESUMEN

Introducción: El brote de DENV de enero a noviembre de 2023 se caracterizó por un aumento en los retrasos en el diagnóstico y tratamiento de diversas afecciones médicas, incluyendo la rickettsiosis, que frecuentemente se manifiesta como una enfermedad febril aguda similar a la fiebre por dengue. Las principales manifestaciones clínicas incluyen fiebre, cefalea, mialgia, confusión mental, dolor abdominal y vómito. **Reporte de caso:** Reportamos un caso de rickettsiosis enmascarada por DENV durante un brote en Yucatán, México, para sensibilizar al personal médico sobre la importancia de considerar la rickettsiosis como parte del diagnóstico diferencial de las enfermedades exantemáticas febriles, especialmente en áreas endémicas de dengue. **Discusión:** Si bien las rickettsiosis tienen manifestaciones específicas, durante su evolución, pueden confundirse con otras enfermedades exantemáticas de la región, por lo que es importante incorporar un estudio sistemático de los determinantes epidemiológicos y ambientales, especialmente en un brote epidemiológico de DENV en áreas endémicas que nos permita realizar un diagnóstico oportuno.

Palabras clave: Rickettsiosis, fiebre, rash, dengue virus

SUMMARY

Introduction: The DENV outbreak from January to November 2023, was marked by increased delays in diagnosis and treatment of a variety of medical conditions including Rickettsiosis that frequently manifests as an acute febrile illness like Dengue. The main clinical manifestations include fever, headache, myalgia, mental confusion, abdominal pain and vomiting. **Case Report:** We report a case of Rickettsiosis masked by DENV during an outbreak in Yucatan, Mexico and to sensitize medical personnel on the importance of considering rickettsiosis as part of the differential diagnosis of febrile exanthematic diseases, especially in DENV endemic areas. **Discussion:** Although Rickettsiosis has specific manifestations, during its evolution, they can be confused with other exanthematic diseases of the region, so it is important to incorporate a systematic study of the epidemiological and environmental determinants, especially in an epidemiological outbreak of DENV in endemic areas that will allow us to make a timely diagnosis.

Keywords: Rickettsioses, fever, rash, dengue virus.

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Fecha de Recepción: 14 de noviembre de 2024

Fecha de Aceptación: 28 de diciembre de 2024

Introducción

Rickettsiosis are diseases caused by bacteria of the *Rickettsia* genus and constitute a serious public health problem worldwide, because they affect the secondary and tertiary sectors of the population. Due to the difficulty of diagnosis, fatal outcomes have occurred because of late intervention in treatment (1). The clinical of rickettsiosis is variable and depends on the patient's conditions, it can be overlooked as a possible diagnosis because its symptoms overlap with those of dengue, leptospirosis, Chikungunya and even COVID-19 (2).

Murine typhus is an acute febrile, flea borne, disease caused by infection with *Rickettsia typhi* (*R. typhi*). This bacterium is maintained in nature through 2 transmission cycles: the classical cycle, in which rats (*Rattus spp.*) act as a reservoir, and their fleas (*Xenopsylla cheopis*) as the main vector, and the peridomestic cycle, where animals such as opossums, cats and dogs can play the role of reservoirs, and the flea *Ctenocephalides felis* as a possible vector. The main route of infection for humans is contact with flea feces, through the conjunctivae, inhalation, or from scabs produced by scratching in the arthropod's bite area (5).

R. typhi has an incubation period of two to 14 days, with an average of seven days, Murine typhus begins with fever, headache, myalgia and arthralgias. Symptoms such as nausea, vomiting, diarrhea and abdominal pain that may resemble an acute abdomen may be added before the onset of exanthema (3). The exanthem is maculopapular with centrifugal distribution, usually appearing 3 to five days after the onset of fever in 90% of patients. Involving the trunk and extremities, involvement of the palms and soles is considered typical, but occurs in only 36% to 82% of patients with the rash (3). When the disease progresses, lymphadenopathies, alterations in the central nervous system such as confusion and nuchal rigidity, eschar at the inoculation site, myalgias and arthralgias, hepatitis, vomiting and cardiovascular instability may appear (4).

In Mexico, the latest reports from the epidemiological surveillance system show an

incidence of 0.8 cases per 100,000 inhabitants, distributed in 87% of the states of the country, with a mortality of 30% in pediatric age (6). Murine typhus (causal agent *R. typhi*) is the second most frequent rickettsia disease, with 2018 and 2019, while Rocky Mountain spotted fever (causal agent *R. rickettsii*) and unspecified rickettsia disease accounted for another 617 and 294 cases, respectively (7).

In Yucatan, the presence of *R. felis*, *R. parkeri*, *R. typhi*, and *R. rickettsii* has been demonstrated in human cases, the latter particularly in pediatric patients (8). Reports of fatal cases of *R. typhi* in children in Yucatan underscore the need to reinforce early diagnosis, due to the nonspecific nature of the signs and symptoms. Especially, in endemic places such as Yucatan where masking with dengue fever has been reported in 40% of cases for more than two decades (9).

Epidemiological data in Yucatan reported a 100% increase in the number of dengue fever cases compared to last year (10). The relevance in the identification of these cases indicates the turn that the clinical spectrum of the disease is beginning to take and forces us to consider this event as a serious warning about the possibility that the appearance of severe cases may manifest itself in an epidemic manner (11).

It is important to continue sensitizing medical personnel on the importance of considering rickettsiosis as part of the differential diagnosis of febrile exanthematous diseases, especially in dengue endemic areas. We report a case of Rickettsiosis masked by DENV during an outbreak in Yucatan, Mexico.

Clinical case presentation

During the outbreak of the DENV in January 2023, an 8-year-old female from a rural area of Felipe Carrillo Puerto, Quintana Roo, previously healthy, with a history of living with a feral dog, began her current illness with fever and erythematous, pruritic macular exanthema in the lower extremities, respecting the soles and palms, generalized colicky abdominal pain and two vomits of gastroalimentary content were added, so she went to her family clinic where she was prescribed trimethoprim sulfamethoxazole



Figure 1. A. Maculopapular exanthem with centripetal distribution in the abdomen and anterior thorax. B. Maculopapular exanthem on the face without respecting the nasolabial triangle, affecting the suprasternal region and cervical region. C. Maculopapular rash on lower limbs.

(40mg/kg/day), levocetirizine (5mg/24 hours) and metamizole sodium (10 mg/kg/dose) for 48 hours, without improvement, she went to our second level unit.

On arrival, fever, erythematous and maculopapular rash located in the thorax, abdomen and lower extremities, with involvement of the soles of the feet, accompanied by generalized abdominal pain, referred to as colicky, without irradiation, with intensity on VAS scale 7/ 10, accompanied by nausea (Figure 1). In hematological studies highlights the presence of leukocytosis at the expense of neutrophils and bandemia with positive acute phase reactants, hyponatremia, without alterations in liver function tests (Table 1).

Abdominal ultrasound reported no alterations at hepatic level, bowel loops with fluid inside, edematous and with increased peristalsis, with data suggesting enteric inflammatory process secondary to antibiotic ingestion, which was managed with *Bacillus clausii* spores four billion orally every 24 hours for five days. As part of the approach to fever and exanthema, blood cultures, urine culture and stool cultures were taken on admission and reported without bacterial growth. Initially dengue was suspected due to the initial clinical manifestations and the

health alert issued in the state of Yucatan about the increase in positive cases of dengue fever in January 2023, however, serology was negative after 48 hours. Given the clinical evolution of the patient and according to epidemiological guidelines and the follow-up protocol for the care of patients with Rickettsiosis, the patient met the criteria of a probable case by operational definition, fever plus rash, abdominal pain, vomiting, as well as the identification of a history of vector bite or contact with dogs in the two weeks prior to the onset of the symptoms. Given the clinical suspicion, it was decided to start empirical treatment with oral doxycycline (4mg/kg/day) to avoid fatal complications. After 24 hours with doxycycline, control laboratories were performed, showing a decrease in the leukocyte count, negative C-reactive protein, liver function tests in normal ranges and slightly increased ESR, abdominal ultrasound was repeated, which was reported without alterations (Table 1).

The diagnosis of rickettsiosis was established using the polymerase chain reaction and sequencing of the fragments of the *ompB* and the *htrA* genes (17kDa protein) (12,13). After removing primer sequences, we compared amplicon sequences by conducting a gapped BLAST 2.0 search of the GenBank database; the

Table 1. Laboratory follow-up during hospitalization.

Variables	Day 1	Day 2	Day 4	Reference values
Blood biometry				
Leukocytes (mm ³)	16.5	13.8	4.7	4.5–10 mm ³
Neutrophils (%)	87.1	85	33.8	37%–73%
Lymphocytes (%)	7.4	9.9	53.0	20%–40%
Bands (%)	6.0	10	0	0–0%
Hemoglobin (g/dL)	12.8	12	12.6	10–15 g/dL
Hematocrit (g/dL)	38.5	36.1	38.2	30–46 g/dL
Platelets (mm ³)	352	336	502	150–400 mm ³
Chemistry				
Total bilirubin (mg/dL)	0.75	0.62	0.3	0.3–1 mg/dL
Direct bilirubin (mg/dL)	0.2	0.2	0.07	0–0.20 mg/dL
Indirect bilirubin (mg/dL)	0.55	0.42	0.23	0.1–0.90 mg/dL
AST (IU/L)	21	12	21	15–41 IU/L
ALT (IU/L)	10	8	11	15–41 IU/L
Lactate Dehydrogenase (U/L)	428	390	312	140–271 U/L
Serum electrolytes				
Sodium (mEq/L)	132.6	133	136.5	135–145 mEq/L
Inflammatory markers				
ESR (mm/hr)	8	12	15	1.0–15.0 mm/hr
CRP (mg/dl)	12	48	0	0–0.75 mg/dL

CRP, C-reactive protein; ALT, alanine aminotransferase or serum glutamate pyruvate transaminase; AST, aspartate aminotransferase or serum glutamic-oxaloacetic transaminase; ESR, erythrocyte sedimentation rate.

ompB and *htrA* genes fragment sequences showed 99% and 98% identity with *R. typhi* strain Wilmington (accession no. AE017197.1).

The patient was discharged home due to improvement on the fifth day of hospital stay, with outpatient management, completing seven days with oral doxycycline. The patient was followed up in the outpatient clinic and was scheduled a month after discharge, control laboratories were taken, in which leukocytes were found in normal ranges, with no alterations in cell lines, negative acute phase reactants, liver function tests in normal ranges and no sequelae at the time of discharge.

Discussion

The clinical of rickettsiosis is variable and can be confused with multiple febrile illnesses such as

dengue fever, leptospirosis, Chikungunya and even COVID-19 (14).

Nonspecific symptoms (fever, myalgias, headache, and rash) overlap between illnesses, including SARS-CoV-2 virus infection, where a case of murine typhus was documented in a 25-year-old man from southern California, with a 4-day history of headache, myalgias, chills, and fever up to 39.2°C, during the first year of the COVID-19 pandemic (2020), where testing for SARS-CoV-2 was performed using nasopharyngeal and oropharyngeal PCR tests that were negative. Initially in his labs with bandemia 20.3% and lymphopenia 0.78×1000/μL, blood culture with no growth at 5 days. He was treated with 1 gram of intramuscular ceftriaxone, was discharged from home with azithromycin for five days, presenting worsening symptoms (15).

Like the clinical case presented here, where the initial suspicion was dengue infection, due to the epidemiological situation (DENV outbreak in January 2023), we found similarities in the initial clinical manifestations such as fever, myalgia, headache, and in the admission laboratories of our patient, since she was found with 6% bandemia and lymphopenia $0.74 \times 1000/\text{ML}$.

Late diagnosis of febrile syndrome has potentially fatal implications, but its nonspecific manifestations, added to the possible simultaneous presence of several agents prevalent in tropical areas, make the diagnostic challenge acquire unknown dimensions (9).

It is important to impact hospital management especially when co-infection by *Rickettsia* species and DENV is present, in the case presented here, as the initial detection of DENV infection stopped the diagnostic algorithm of febrile exanthematous disease, doxycycline was not initiated in the first 5 days of the disease, until the seventh day in which due to ventilatory and hemodynamic deterioration, the positive test for *Rickettsia* was obtained and management with doxycycline was initiated, however, the patient presented electrical activity without pulse, warranting resuscitation maneuvers, without return to circulation. This case emphasizes the need for diagnostic protocols for febrile exanthematous disease in areas endemic for DENV, CHKV, ZKV and *Rickettsiosis* (16).

Especially in Yucatan, where the presence of murine typhus has been recognized since 2005, especially in the pediatric population with a case fatality rate of 33.5% (17) and where sequelae affecting the quality of life of patients have been described, as has also occurred in Sonora, Mexico (18).

Conclusion

Rickettsiosis are febrile exanthematous infectious diseases that in the last decade have decreased their mortality in pediatric patients thanks to timely diagnosis and treatment. In Yucatan they continue to be a challenge for physicians at all levels of care, since initially the symptoms overlap with those of other endemic

diseases, such as DENV. Therefore, laboratory diagnosis of *Rickettsia* species should be routinely considered as a differential diagnosis when studying a pediatric patient with fever and exanthema, with emphasis on looking for environmental and epidemiological determinants in the interrogation that support the clinical suspicion. Physicians should be kept aware, especially in endemic areas and in the face of outbreaks of diseases of major media interest such as DENV.

Funding

This work was supported by Consejo Nacional de Ciencia y Tecnología (CONACyT) grant FOSISS 261885.

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