Tropical Biomedicine 39(4): 575-578 (2022)
https://doi.org/10.47665/tb.39.4.014

SHORT COMMUNICATION

Unusual co-infection of severe malaria by *Plasmodium vivax* and dengue virus in Mexico

Queb-Pech, N.M.[1], Núñez-Oreza, L.A.[2], Estrada-Méndez, A.[1], Tamay-Segovia, P.[3], Collí-Heredia, J.P.[1], Blum-Domínguez, S.C.[4*]

[1]Departamento de Medicina Interna, Hospital General de Especialidades "Dr. Javier Buenfil Osorio", 24097 San Francisco de Campeche, Campeche, México
[2]Laboratorio de Microbiología y Biología Molecular, Centro de Investigaciones Biomédicas, Universidad Autónoma de Campeche, 24039 San Francisco de Campeche, Campeche, México
[3]Laboratorio de Enfermedades Transmitidas por Vectores y Zoonosis, Centro de Investigaciones Biomédicas, Universidad Autónoma de Campeche, 24039 San Francisco de Campeche, Campeche, México
[4]Laboratorio de Enfermedades Tropicales, Centro de Investigaciones Biomédicas, Universidad Autónoma de Campeche, C.P. 24039 San Francisco de Campeche, Campeche, México
*Corresponding author: selblum@hotmail.com

ARTICLE HISTORY

Received: 5 September 2022
Revised: 7 December 2022
Accepted: 7 December 2022
Published: 31 December 2022

ABSTRACT

Malaria and dengue fever are among the most common mosquito-borne diseases worldwide; however, reports of coinfection are rare. We present a case of severe malaria and dengue coinfection in a 16-year-old female patient presenting with fever, thrombocytopenia, pleural effusion, myopericarditis, and acute respiratory distress syndrome. Dengue infection was confirmed by the presence of immunoglobin M antibodies and nonstructural protein 1, while malaria was confirmed by the presence of *Plasmodium vivax* in thick and thin blood smears. This is the first report of a dengue/malaria coinfection in Mexico.

Keywords: Co-infection; Dengue; Malaria.

INTRODUCTION

Malaria and dengue fever are the most important mosquito-borne diseases in endemic areas of Central and South America; they significantly affect public health due to their high morbidity and mortality (Wiwanitkit, 2011). Dengue is a viral infection that is prevalent in Mexico and other Latin American countries, including Brazil, Honduras, and Colombia (Arredondo-García *et al*., 2018). Despite vector prevention and control efforts, the persistence of dengue viral outbreaks makes it a major public health concern in Mexico (Organización Panamericana de la Salud, 2008). Malaria is a parasitic disease caused by several *Plasmodium* species. In 2018, there were 614 cases of malaria caused by *Plasmodium vivax* in Mexico, three of which occurred in the state of Campeche, specifically in the municipalities of Candelaria, Escárcega, and Campeche. In 2019, Mexico reported 618 cases of malaria caused by *P. vivax*, two of which occurred in Candelaria (Sistema Estatal de Vigilancia Epidemiológica, 2019).

Although cases of coinfection with malaria and dengue have been reported, they are rare (Carme *et al*., 2009; Chong *et al*., 2017). A comprehensive literature review confirmed that this is the first case report of *P. vivax* and dengue virus coinfection in Mexico.

CASE PRESENTATION

A 16-year-old female Guatemalan patient residing in Candelaria, Campeche, Mexico, was admitted to the Hospital of Candelaria on March 13, 2021, reporting 3 days of symptom evolution involving headaches, myalgia, and fever. Although the patient had no relevant medical history, she referred to a trip to a refugee camp at the Guatemala-Mexico border 7 days before the symptoms developed. During the general physical examination, the patient had signs of mosquito bites in multiple anatomical areas. She was conscious, drowsy, and tachycardic (151 bpm), with a blood pressure of 85/58 mmHg and abdominal pain upon hypogastrium palpation. Blood test results revealed anemia (hemoglobin 11.6 g/dL, normal values 12.0 a 16.0 g/dL) and thrombocytopenia (platelet count 68 × 10^9/L, normal values 150 a 450 × 10^3/µL), suggesting dengue virus infection. As the patient presented clinically in a shock state, she was initially treated with crystalloids and antipyretics according to guidelines for dengue treatment; however, as there was no improvement, she was transferred to the General Hospital of Specialties of Campeche 3 days after admission to Candelaria Hospital. Given the persistence of fever, headache, abdominal pain, and cough, follow-up controls with complete blood count were performed. The results of the laboratory tests again showed anemia (hemoglobin 10.8 g/dL, normal values 12.0 a 16.0 g/dL), a hematocrit of 31.16% (normal values 38 a 48%), severe thrombocytopenia (platelet count 32.2 × 10^9/L, normal values 150 a 450 × 10^3/µL), and a normal leukocyte count (white blood cell count 8.3 × 10^3/µL, normal values 5.0 a 10.0 × 10^3/µL). Normal renal function was observed, with an urea of 17.1 mg/dL (normal values 15 a 45 mg/dL) and a serum creatinine of 0.61 mg/dL (normal values 0.60 a 1.10 mg/dL). Liver function was mildly impaired, with a total bilirubin of 1.3 mg/dL (normal values until 1.10 mg/dL), direct bilirubin 0.9 mg/dL (normal values until 0.25 mg/dL), and alanine aminotransferase (ALT) 49 U/L (normal values

at 30°C up to 22 U/L); the aspartate aminotransferase (AST) level was normal (32 U/L). Reverse transcription-polymerase chain reaction and antigen tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were negative. On the other hand, nonstructural protein 1 (NS1) and immunoglobin M (IgM) dengue serology (Certum Dengue Combo Ab[IgG + IgM] + Ag[NS1] commercial kit, China; an immunochromatographic rapid test that detects NS1 protein and IgG/IgM dengue antibodies) was performed. NS1 and IgM dengue serology were positive 6 days after symptom onset, confirming the diagnosis of severe dengue fever.

Throughout the patient's stay at the General Hospital of Campeche (2 days after admission), the patient experienced periodic fever spikes every 48 hours and developed dyspnea and polypnea. An oxygen experienced of 74% necessitated supplemental oxygen and noninvasive mechanical ventilation. Chest computed tomography revealed bilateral pleural effusion and bilateral pulmonary opacities with septal thickening (Figure 1); because these findings were consistent with a severe dengue fever presentation, no pleural puncture was performed as respiratory mechanics improvement with noninvasive mechanical ventilation and colloidal solution (albumin 25%) administration. The patient had an arterial blood gas pH of 7.5 (normal values 7.35 a 7.45), partial pressure of carbon dioxide (pCO_2) of 25 mmHg (normal values 35 a 45 mmHg), partial pressure of oxygen (pO_2) of 75 mmHg (normal values 80 a 100 mmHg), lactate concentration of 1.7 mmol/L (normal values 0.5 a 2.2 mmol/L), bicarbonate (HCO_3) concentration of 19 mmol/L, (normal values 22 a 26 mmol/L), and an arterial oxygen pressure/fraction of inspired oxygen (PaO_2/FiO_2) index of 187 mmHg (normal values over 300 mmHg). Two-dimensional echocardiography revealed anteroseptal hypokinesia, a global longitudinal strain of -16.5%, left ventricular ejection fraction of 62%, and pericardial effusion of 50 cc. Cardiac troponin I was evaluated and yielded a normal result of 0.028 ng/mL. Given the persistence of the fever, biological samples were sent to the Biomedical Research Center of the University of Campeche to exclude leptospirosis. Blood and urine samples were negative by direct search on dark field microscopy and polymerase chain reaction. Therefore, a Dengue IgG/IgM/NS1 Combo Test Cassette assay (Xiamen Boson Biotech Co., Ltd. P. R. of China) a rapid chromatographic immunoassay for detecting dengue NS1 and IgG and IgM antibodies against the virus to distinguish between primary and secondary infection) was performed on day 9 after symptom appearance. The results were positive for NS1 protein and IgM antibodies against dengue virus, indicating a recent and active primary dengue infection. In addition, malaria was suspected due to the periodic peaks of fever every 48 hours in the patient. Thin and thick blood smears were stained on glass slides on day 9 post-onset of symptoms and revealed the presence schizonts of *P. vivax* (Figure 2).

The patient was treated with 0.5 mg/kg/day primaquine, 10 mg/kg/day chloroquine on day 1 of treatment, and 5 mg/kg/day chloroquine on days 2–5 of treatment after the positive malaria test. Following the initiation of treatment, she demonstrated progressive clinical and biochemical improvement. On the fourth day of treatment (day 7 from admission), the patient left the hospital against medical advice. At the time of discharge, laboratory results revealed that the patient had a hemoglobin of 11.55 g/dL, hematocrit of 35.2%, platelet count of 60.16 × 10^9/L, leukocyte count of 6.936 × 10^3/µL, creatinine of 0.57 mg/dL, urea of 42.8 mg/dL, total bilirubin of 1.3 mg/dL, ALT of 22 U/L and AST of 29 U/L.

Confidentiality of the data

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

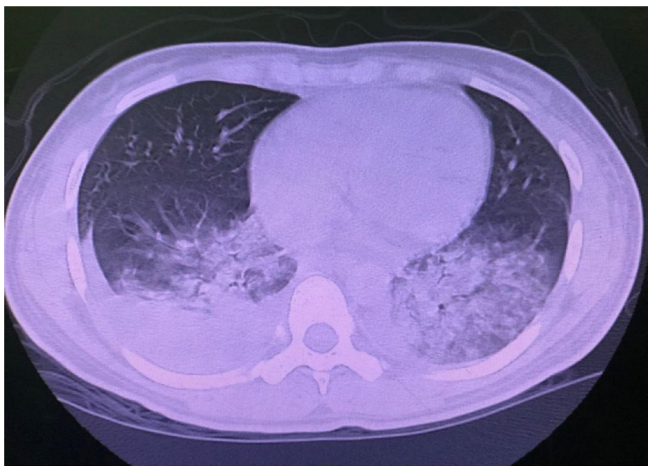

Figure 1. Chest computed tomography demonstrates smooth interstitial thickening, bilateral ground-glass opacities, and mild pericardial and pleural effusions (right greater than left).

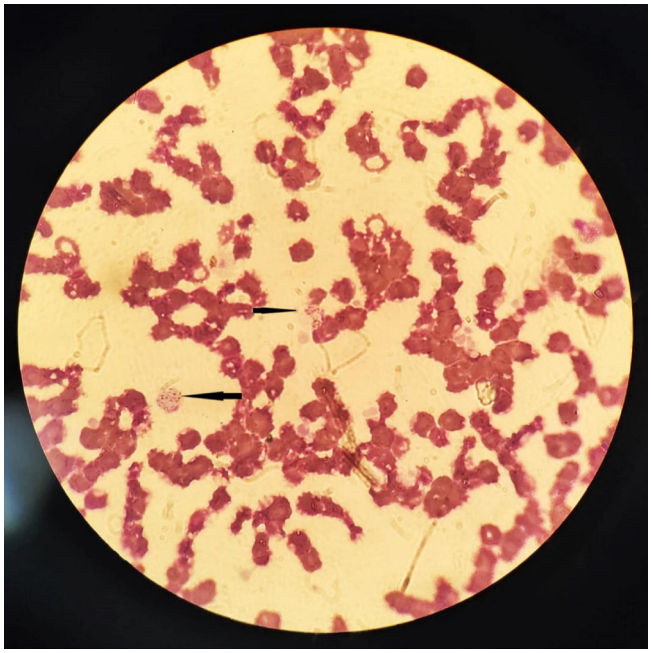

Figure 2. Microscopic examinations of a peripheral blood smear of *Plasmodium vivax* infection (Wright's staining, ×1000).

Right to privacy and informed consent

The authors obtained the informed consent of the patient referred to in the case report; 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

There have been few reports on malaria and dengue coinfection since the publication of the first case by Charrel *et al*. (2005) and Bygbjerg *et al*. (2018). However, there is likely a prevalence of coinfection in tropical environments that is not being reported despite the presence of both infectious agents (Carme *et al*., 2009). Our case involved a patient living in a tropical region where dengue

virus and *Plasmodium* coexist. Fever, headache, fatigue, and joint pain are common symptoms of both infections (Gupta *et al*., 2017). Diagnosis of coinfection based solely on clinical presentation is difficult due to the similar clinical features of these diseases, which may account for the lack of reports on coinfections (Bygbjerg *et al*., 2018). Another factor contributing to the underreporting of coinfections could be the differential distribution of the *Aedes* and *Anopheles* mosquitoes. As the species are not expected to be found together, infection by the distinct pathogens is rarely assumed (Wiwanitkit, 2011).

Laboratory tests are necessary for definitive diagnosis. In our patient, dengue-specific IgM antibodies and NS1 were detected on the sixth day after symptom onset. NS1 detection suggested a recent infection (Suleman *et al*., 2016). In addition, the patient reported having a fever 3 days prior to admission and demonstrated a lack of IgG reactivity, indicating that she had not been previously infected. Severe dengue fever was suspected as the primary diagnosis; over the course of clinical development, the patient's fever persisted even after the assumed critical period, and respiratory deterioration and hemolysis were observed. Malaria was suspected due to the periodicity of the fever and epidemiological associations, and the diagnosis was confirmed by the presence of *P. vivax*.

Malaria infections can range from non-severe to severe, with an increasing risk of serious complications, including cerebral malaria, severe anemia, respiratory distress, and kidney failure (Cabezón-Estévanez & Hernández-Mora, 2016). In this case, the patient presented with pleural effusion and acute respiratory distress syndrome, which occur in 1–10% of cases infected with *P. vivax*. This severe presentation of malaria is uncommon, with pulmonary symptoms more often observed in pediatric patients (Taylor *et al*., 2012). The malaria parasite has tropism for myocardial tissue and has been reported to cause myocardial dysfunction. Cardiovascular complications can coincide with other fatal complications, including pulmonary manifestations and circulatory collapse. Severe malaria can lead to specific cardiac complications, with reports describing conduction disorders, arrhythmias, myocarditis, pericarditis, cardiogenic shock, and heart failure (Gupta *et al*., 2021). Increased severity is associated with *Plasmodium falciparum* infection but has also been reported for *P. vivax* (Maguire *et al*., 2007; Bustos *et al*., 2014), such as the case described in this report. The pathogenic mechanisms differ between the two infections; malaria is primarily characterized by anemia due to significant intravascular hemolysis (Mendonça *et al*., 2015), while thrombocytopenia and fluid leakage are the major features of dengue fever. Notably, coinfections increase the incidence of severe thrombocytopenia, as observed in our patient (Epelboin *et al*., 2012; Mendonça *et al*., 2015). In this case, both pathologies were characterized as serious due to the clinical manifestations and laboratory findings, which included shock, lung involvement, prostration, myopericarditis, anemia, and thrombocytopenia (PAHO, 2022; WHO, 2022).

Other studies on dengue and severe malaria coinfection reported a low hematocrit value, similar to what was found in our clinical case. An alarm sign for severe dengue fever is a high hematocrit value, which can be confusing when establishing criteria for severe dengue (Magalhães *et al*., 2014). However, in this type of coinfection, patients present with anemia, which is observed in malaria but not in dengue fever. Therefore, the anemia caused by *P. vivax* explains the low hematocrit concentration. It is difficult to diagnose the severity of dengue fever due to its clinical manifestations, which have been reported to be similar in both concurrent infection and monoinfection (Aruchana *et al*., 2016).

No specific treatment is recommended for patients with concurrent infection. Moreover, there is no specific treatment for severe dengue fever (PAHO, 2022; WHO, 2022). Otherwise, specific treatment for pleural effusion due to plasma leakage is only preventive, supportive with positive pressure, or in case of respiratory deterioration, pleural puncture is considered.

Patients with dengue fever are treated based on their symptoms, and antimalarial drugs are prescribed according to the parasite species and the disease severity. In this case, the antimalarial regimen recommended by the guidelines of the National Center of Preventive Programs and Disease Control in M¹xico were followed.

Due to a high prevalence of dengue in this area, dengue virus infection was initially suspected. However, coinfection with dengue virus and *Plasmodium* species may frequently occur in tropical and subtropical areas where these diseases coexist. In such regions, both pathologies should be considered to ensure timely diagnosis and treatment.

ACKNOWLEDGEMENT

Thanks to Dr Edgar Daniel Godínez Tamay, for their support to carry out this study.

Conflict of interest

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

REFERENCES

Aruchana, A.P.S., Priyadarshi, S.S., Madhusmita, S. & Stephen, A. (2016). A review of concurrent infections of malaria and dengue in Asia. *Asian Pacific Journal of Tropical Biomedicine* **6**: 633-638. https://doi.org/10.1016/j.apjtb.2016.05.008

Arredondo-García, J.L., Aguilar-López Escalera, C.G., Aguilar Lugo-Gerez, J.J., OsnayaRomero, N., PérezGuillé, G. & Medina-Cortina, H. (2020). Panorama epidemiológico de dengue en México 2000-2019. *Revista Latinoamericana de Infectologɑa Pediátrica* **33**: 78-83. https://doi.org/10.35366/94418

Bustos, M.M., Gómez, R., Álvarez, C.A., Valderrama, S. & Támara, J.R. (2014). Síndrome de dificultad respiratoria aguda del adulto por *Plasmodium vivax*. *Acta Medica Colombiana* **39**: 211-215.

Bygbjerg, I.C., Simonsen, L. & Schiøler, K.L. (2018). Elimination of falciparum malaria and emergence of severe dengue: An independent or interdependent phenomenon? *Frontiers in Microbiology* **9**: 1120. https://doi.org/10.3389/fmicb.2018.01120

Cabezón-Estévanez, I. & Hernández-Mora, M.G. (2016). Actualización de las complicaciones pulmonares de la malaria. *Medicina Clínica* **146**: 354-358. https://doi.org/10.1016/j.medcli.2015.11.043

Carme, B., Matheus, S., Donutil, G., Raulin, O., Nacher, M. & Morvan, J. (2009). Concurrent dengue and malaria in Cayenne Hospital, French Guiana. *Emerging Infectious Diseases* **15**: 668-671. https://doi.org/10.3201/eid1504.080891

Charrel, R.N., Brouqui, P., Foucault, C. & de Lamballerie, X. (2005). Concurrent dengue and malaria. *Emerging Infectious Diseases* **11**: 1153-1154. https://doi.org/10.3201/eid1107.041352

Chong, S.E., Mohamad R.H., Suraiya, S., Lee K.T. & Lim J.A. (2017). The dangers of accepting a single diagnosis: case report of concurrent *Plasmodium knowlesi* malaria and dengue infection. *Malaria Journal* **16**: 2. https://doi.org/10.1186/s12936-016-1666-y

Epelboin, L., Hanf, M., Dussart, P., Ouar-Epelboin, S., Djossou, F., Nacher, M. & Carme, B. (2012). Is dengue and malaria co-infection more severe than single infections? A retrospective matchedpair study in French Guiana. *Malaria Journal* **11**: 142. https://doi.org/10.1186/1475-2875-11-142

Gupta, N., Gupta, C. & Gomber, A. (2017). Concurrent mosquito-borne triple infections of dengue, malaria and chikungunya: A case report. *Journal of Vector Borne Diseases* **54**: 191-193.

Gupta, S., Gazendam, N., Farina, J.M., Saldarriaga, C., Mendoza, I., López-Santi, R., Pérez, G.M., Martínez-Sellés, M. & Baranchuk, A. (2021). Malaria and the heart: JACC S state of the art review. *Journal of the American College of Cardiology* **77**: 1110-1121. https://doi.org/10.1016/j.jacc.2020.12.042

Magalhães, B.M., Siqueira, A.M., Alexandre, M.A., Souza, M.S., Gimaque, J.B., Bastos, M.S., Figueiredo, R.M., Melo, G.C., Lacerda, M.V. & Mourão, M.P. (2014) *P. vivax* malaria and dengue fever co-infection: a cross-sectional study in the Brazilian Amazon. *PLoS Neglected Tropical Diseases* **8**: e3239. https://doi.org/10.1371/journal.pntd.0003239

Maguire, J.D., Fenton, M.E., Susanti, A.I. & Walker, J.B. (2007). *Plasmodium vivax*-associated acute respiratory distress syndrome after extended travel in Afghanistan. *Travel Medicine and Infectious Disease* **5**: 301-305. https://doi.org/10.1016/j.tmaid.2007.04.001

Mendonça, V.R.R., Andrade, B.B., Souza, L.C.L., Magalhães, B.M.L., Mourão M.P.G., Lacerda, M.V.G. & Barral-Netto, M. (2015). Unravelling the patterns of host immune responses in *Plasmodium vivax* malaria and dengue co-infection. *Malaria Journal* **14**: 315. https://doi.org/10.1186/s12936-015-0835-8

Organización Panamericana de la Salud/Organización Mundial de la Salud. 142. Sesión del Comité Ejecutivo. Dengue: Informe sobre la situación actual. https://iris.paho.org/bitstream/handle/10665.2/6118/ce14217s.pdf?sequence=2&isAllowe=y. Accessed 18 de june202.

Pan American Health Organization (PAHO). (2022). PAHO Guidelines for the Clinical Diagnosis and Treatment of Dengue, Chikungunya, and Zika. Washington, D.C.: Pan American Health Organization. License: CC BY-NC-SA 3.0 IGO. https://doi.org/10.37774/9789275124871

Sistema Estatal de Vigilancia Epidemiológica- Instituto de Servicios Descentralizados de Salud Pública del Estado de Campeche (2019). Boletín Epidemiológico No. 27. 2019. Secretarɒa de Salud. http://www.campeche.salud.gob.mx/index.php/boletin-epidemiologico. Accessed 15 december 2022

Suleman, M., Faryal, R., Alam, M.M., Sharif, S., Shaukat, S., Aamir, U.B., Khurshid, A., Angez, M., Umair, M., Sufian, M.M. *et al*. (2016). NS1 antigen: A new beam of light in the early diagnosis of dengue infection. *Asian Pacific Journal of Tropical Medicine* **9**: 1212-1214. https://doi.org/10.1016/j.apjtm.2016.10.007

Taylor, W.R.J., Hanson, J., Turner, G.D.H., White, N.J. & Dondorp, A.M. (2012). Respiratory manifestations of malaria. *Chest* **142**: 492-505. https://doi.org/10.1378/chest.11-2655

Wiwanitkit, V. (2011). Concurrent malaria and dengue infection: A brief summary and comment. *Asian Pacific Journal of Tropical Biomedicine* **1**: 326-327. https://doi.org/10.1016/S2221-1691(11)60053-1

World Health Organization (WHO). (2022). WHO guidelines for malaria, 3 June 2022. *World Health Organization*. https://apps.who.int/iris/handle/10665/354781. License: CC BY-NC-SA 3.0 IGO. Accessed 5 july 2022.