


Concurrent Dengue-Malaria Infection: The Importance of Acute Febrile Illness in Endemic Zones

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ABSTRACT

CONTEXT: Acute febrile disease (AFI) in endemic tropical areas is a frequent reason for consulting the emergency services. Infection by 2 or more etiological agents may modify clinical and laboratory parameters, making diagnosis and treatment a challenge.

CASE REPORT: We report the case of a patient who came from Africa and consults in Colombia, with AFI with thrombocytopenia that was eventually diagnosed to have concurrent infection with *Plasmodium falciparum* malaria and dengue.

CONCLUSIONS: Dengue-malaria coinfection reports are scarce; it should be suspected in patients living or returning from areas where both diseases are endemic or during dengue outbreaks. This case serves as a reminder of this important condition that causes high morbidity and mortality if it is not early diagnosed and treated.

KEYWORDS: Acute febrile illness, malaria, coinfection, *Plasmodium falciparum*, dengue virus, thrombocytopenia

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Introduction

Acute febrile illness (AFI) refers to a morbid state of sudden onset of fever, of less than 7 days with evolution, in patients between 5 and 65 years of age, in which no signs or symptoms related to an apparent infectious focus have previously been identified. In Colombia, more than 85% of the national territory is located below 1600m above sea level, allowing more than 80 compatible and infectious-contagious diseases whose endemic-epidemic behavior could participate in the etiology of AFI.¹ In this group, microorganisms that produce bacterial, parasitic, and viral infections such as *Leptospira* spp., *Plasmodium* spp. (*falciparum* specially), hepatitis B, dengue virus, chikungunya virus, among others, stand out,¹ making a differential diagnosis necessary, to avoid complications, and redirect early therapeutic measures assertively.

Vector-borne diseases (VTE) represent 17% of all infectious diseases and generate more than 1 million deaths worldwide: mainly in tropical and subtropical regions.² In Colombia the situation is worrying, since some of them are considered persistent endemic-epidemic conditions (malaria, dengue, Chagas disease, and leishmaniasis).^{1,3} According to the Ministry of Health, in Colombia during 2020, 76 958 cases of malaria were registered, of which 98.5% correspond to cases of uncomplicated malaria, the rest to complicated malaria. Infection by *Plasmodium vivax* predominates, with 49.8%, followed by *Plasmodium falciparum* with 49.4%, and mixed infection with 8%. In epidemiological week 52 of 2021, 1823

cases of dengue were reported: 719 cases from that week and 1104 cases from previous weeks. So far in 2021, 53 334 cases of dengue were reported in the Ministry of Health system, 25 814 (48.4%) without warning signs, 26 562 (49.8%) with warning signs, and 958 (1.8%) with severe dengue.

Malaria is caused by 5 different species of protozoan parasite, *Plasmodium*. These include *P. falciparum*, *P. ovale*, *P. malariae*, *P. vivax*, and *P. knowlesi* that are carried and spread by Anopheles mosquito.⁴ Dengue is a mosquito-transmitted virus, the primary vectors of the disease are female mosquitoes of the species *Aedes aegypti* and *Aedes albopictus*.⁵ Dengue fever is caused by any of the 4 serotypes DENV-1, 2, 3 and 4.⁵ DENV5 and other *Aedes* spp. are also contributed for DENV.⁵ In recent decades, an increase in the concurrent circulation of cases caused by the dengue virus and malaria (*Plasmodium falciparum*) in the same region have been reported.^{6,7} However, concurrent infections are still considered rare and are infrequently reported.⁸

Concurrent infections can include more than 1 pathogen, which can complicate diagnosis and sometimes be associated with greater severity or a change in the clinical course of the disease. Due to the clinical similarities and the overlapping endemicity, they may finally result in a sub-diagnosis of a concurrent infection.^{3,8}

To date, there are few reports of Malaria/Dengue described for Colombia. We present the case of a patient with AFI and thrombocytopenia in which a diagnosis of concurrent malaria and dengue infection was established.



Table 1. Clinical examinations performed on the patient.

CLINICAL EXAMINATIONS	1 DAY	3 DAYS	REFERENCE RANGES
Hematocrit	41	34.4	36.0%-46.0%
Hemoglobin	10	12	12-14 g/dl
White blood cell count	6010	5350	4000-11 000/mm ³
Platelet count	97 000	137 000	150 000-400 000/mm ³
Serum creatinine	0.86		0.51-0.95 mg/dl
Ureic nitrogen			12-26 mg/dl
Serum alanine transferase	133	85	0-32 U/L
Serum aspartate aminotransferase	57	25	0-33 U/L
Dengue IgM (rapid test)	Positive		
Dengue IgG (rapid test)	Positive		
Thick blood film	Positive for <i>P. falciparum</i>		
Thromboplastin time	36.3	41.2	25 to 35 seconds
Prothrombin time	13.9	13.8	11 to 13.5 seconds

Case Description

A 34-year-old male patient returned to a rural region of Colombia on 17 December 2020, from Africa, where he lived for 10 months in the city of Gul, Uganda. He went to the emergency room on 26 December 2020 due to 10-day history of fever, holocranial headache, myalgia, arthralgia, and retroocular pain associated with sudden onset epistaxis and choluria. Physical examination revealed blood pressure 110/80 mmHg, heart rate 89 beats/minute, respiratory rate 16 breaths/minute, temperature 39°C, oxygen saturation 97% room air, cold and sweaty skin without jaundice or skin lesions, with adequate ventilatory dynamics, with hepatosplenomegaly 5 cm below the costal margin, and without any neurological compromise.

Laboratory analysis showed anemia (hemoglobin 10 g/dl reference value 12-14 mg/dl), thrombocytopenia (platelets 97 000/mm³ reference value 150 000-400 000/mm³) and abnormal serum transaminase. Various laboratory investigations were conducted to exclude any other likely cause of the fever and presence of an infection, including those for hepatitis B surface antigen and hepatitis C antibody, both came out normal. Serologic tests for dengue performed on the acute-phase serum (collected 10 days after onset of symptoms) showed the presence of immunoglobulin (Ig) M (titers 1:800) and IgG (titers 1:400; Table 1). Diagnosis of dengue virus infection with warning signs (Group B) was made and admitted to hospitalization for management with intravenous hydration, antipyretic, and total abdominal ultrasound. Ultrasound scan shows pleural effusion in addition to moderate free fluid in the peritoneal cavity surrounding urinary bladder and gallbladder wall thickening, hepatomegaly, splenomegaly, and pleural effusion. A 72 hours after admission, the patient persisted with fever and presented a decrease in

hematocrit (34.4%) with an increase in hemoglobin 12 g/dL and platelets to 137 000/mm³ (Table 1).

Although dengue virus infection had been diagnosed, parasitic tests were performed because the patient had returned from an endemic country with persistent prolonged febrile syndrome, a thick and thin blood smear stained with Giemsa was performed and revealed the characteristic intraerythrocytic ring forms of *Plasmodium falciparum* (trophozoites: a total of 215 000 parasites/ μ l, parasitemia index of 2.3% and gametocytes), which confirmed the diagnosis of malaria as uncomplicated. Antimalarial management was started with artemether-lumefantrine 20/120 mg twice a day for 3 days. To rule out false positives, the asexual parasites load was performed on the peripheral blood smear and MAC-ELISA (considering more than 5 days illness) was positive for dengue virus type 2 (DENV-2). The MAC-ELISA is based on capturing human IgM antibodies on a microtiter plate using anti-human-IgM antibody followed by the addition of dengue virus antigens. The antigens used for this assay are derived from the envelope proteins of the 4 dengue virus serotypes (DENV-1-4).⁹ Considering IgG detection by ELISA in a single serum sample is not useful for diagnostic testing because it remains detectable for life after a dengue virus infection,⁹ the patient was asked if he had had dengue infection before, which he denied, and IgG was negative. Therefore, a diagnosis of concurrent malaria and dengue infection was established.

The patient completed antimalarial treatment with clinical and paraclinical improvement, afebrile, without new episodes of epistaxis or obvious bleeding, without skin lesions or jaundice, normalization of platelets and transaminases with normal total abdominal ultrasound. PCR (molecular test) was performed to confirm the presence of dengue virus in the blood, being positive. After 7 days at hospital, he was fully discharged.

Discussion

In the present study, a dengue and malaria concurrent infection was documented in an endemic tropical zone of Colombia. In Colombia, malaria and dengue are prevalent vector-borne diseases that shared symptoms and endemic profiles.¹

According to what has been reported in the literature, the clinical presentation of this concurrent infection is usually more severe than individual infections, requiring hospitalization for prolonged persistent fever that reaches values of even 40°C.^{7,8} It has been described that in concurrent infection, patients present severity criteria for either of the 2 diseases;⁷⁻⁹ dengue usually spontaneous bleeding, vomiting, and abdominal pain; while for severe malaria criteria the most common is jaundice greater than 3 mg/dl.⁷ In this case, the patient required hospitalization for prolonged AFI, meeting the severity criteria for dengue.

The coexistence between dengue and malaria involves the coexistence of different vectors and hosts who maintain contact with them or travel to different geographic areas where they are present,¹⁰ as was the case of the patient who was on the African continent for 10 months and traveled to Colombia, with the onset of symptoms the days after his arrival. However, overlapping epidemiology, vector distribution, pathogen cocirculation in the same geographic areas, and even initial clinical manifestations; makes it difficult to identify cases of concurrent infections.^{11,12} Hence, having a high index of clinical suspicion for concurrent infection is essential to make a timely diagnosis and administration of the specific treatment required.⁹ Revised literature mentioned that dengue fever should be suspected if a patient presents with bleeding manifestations, retrobulbar headache, severe myalgias, and/or thrombocytopenia.⁸⁻¹³ If suspected, the possibility of mixed infections with various *Plasmodium* species should be excluded to ensure a better treatment outcome.⁸⁻¹³

The absence of differences between concurrent infection and any type of mono-infection with respect to other clinical characteristics, such as joint pain and retroorbital pain, makes it difficult to predict whether febrile patients confirmed with malaria could be concurrent infected with dengue and vice versa.^{7,11} However, the clinical features of concurrent infection are more like dengue mono-infection than malaria mono-infection.⁷

Concurrent infections can have fatal consequences, henceforward the importance of taking a clinical approach with adequate and timely diagnostic tests that guarantee their treatment.³ Immune-mediated or direct interactions in concurrent VTE infections could enhance or inhibit the progression of both infections.¹¹ The diagnosis of 1 type of infection should not exclude the presence of another whose treatment could be ignored or, at least, delayed.^{10,11}

It should be mentioned that the main symptom the patient presented was fever, which is a common reason for consultation in endemic regions.¹ In approach to AFI with a presumptive diagnosis of tropical disease, tests aimed at the most probable

etiologies should be carried out, considering anamnesis, travel history, complete physical examination while evaluating the different semiological aspects, and/or cardinal signs to find diagnostic keys in the proper approach of syndromic and differential diagnoses.¹

In relation to laboratory parameters, a meta-analysis revealed a significant decrease in platelet and leukocyte count without anemia in concurrent infected patients compared to mono-infected malaria patients,¹¹ while dengue mono-infected patients had thrombocytopenia, leukopenia, and hemoconcentration.¹⁰ Furthermore, in patients with concurrent infection, there are no significant changes in hematocrit compared to those with dengue mono-infection.⁸ It should be noted that liver damage is less frequent in co-infection compared to dengue mono-infection.¹⁰ Nevertheless, a cross-sectional study conducted in Brazil observed that the concurrent infected patients had a higher incidence hepatic manifestation such as hepatomegaly, and jaundice (vs dengue mono-infected).^{7,11}

In the described case, the patient did not take in any moment prophylactic medication while in Uganda or Colombia and he denied using bed netting nor prevention strategies. He presented with leukopenia, thrombocytopenia, and anemia initially compatible with dengue with warning signs; but the history of travel along with the persistence of symptoms made it necessary to rule out concurrent infection. Additionally, hepatosplenomegaly could be the result of:

(1) Liver injury due direct viral toxicity where hepatocytes and Kupffer cells are prime targets for dengue infection and dysregulated immunologic injury (T cell mediated process involving interaction between antibodies and the endothelium and a concomitant cytokine storm) in response to the virus.¹⁴

(2) Splenomegaly is associated with cellular expansion in the red and white pulp due to their prominent role during malaria infection. It is tasked with sensing and removing *Plasmodium* parasitized red blood cells, erythropoiesis, the activation and differentiation of adaptive immune cells, and the development of protective immunity.¹⁵

In the case of malaria, confirmation was rapid through a thick and extended drop of peripheral blood performed by professionals from the Hospital Medical Center laboratory. Dengue virus tests can be performed in 2 stages of the disease, during the first 5 days of illness, through the NS1 antigen; after that period serological tests are needed (IgM collection).^{5,16} It is worth to mention that IgM antibodies against dengue increased during the first 3 days after infection and can remain detectable for 3 months or longer after infection,¹⁶ meanwhile dengue IgG antibodies appear after IgM, approximately at the day 7 of the fever, in the primary infection and persist for a longer time, even up to years¹⁶. Table 2. PCR (molecular test) is necessary as a detection of dengue nucleic acid in blood confirms more acute infection and not serological tests that may remain positive from prior infection. Knowing the course of the disease and its relationship with serological, viral, and hematological parameters allows for timely confirmation.^{11,16}

Table 2. Dengue antibody testing interpretation.

IGM RESULTS	IGG RESULTS	POSSIBLE INTERPRETATION
Positive	Negative	Current primary infection
Positive	Positive	Current secondary infection
Low or negative or not tested	Fourfold increase in samples taken 2 to 4 weeks part	Recent infection
Low or negative	Positive	Past infection
Negative	Negative	Too soon after initial exposure for antibodies to develop or symptoms due to another cause.

The presence of cross-reactions has been reported in patients with VTE or previous infections, so the positivity in combination of these studies (dengue-malaria) makes it necessary to confirm dengue disease.^{1,11} This means, dengue serology can be non-specific and further confirmatory testing with a more specific test (RT-PCR) is beneficial regardless of co-infection.^{1,11} Additionally a convalescent serology test would have been helpful to further confirm the diagnosis of dengue. It should be noted that frequently, due to the suspected diagnosis of multiple VTEs and diagnostic confirmation from some agent, health personnel sometimes do not request the confirmatory test, and the other entity is discarded, limiting the possibility of investigating these emerging and highly important arboviruses at the local, regional, and national levels.¹¹ In effect, this limits the opportunity to recognize an emerging epidemiological event from another endemic country.¹⁷

Understanding the concurrent infection by *Plasmodium* spp and DENV is crucial for the design and management of treatment strategies for serious diseases and their complications.¹⁰ In this case report, the detection of positive IgG is relevant; probably indicating a previous exposure to any of the 4 circulating dengue virus serotypes in Colombia or Africa, including a different circulating serotype in Africa and non-circulating in Colombia. On the other hand, it could correspond to immunological memory from previous infections.^{5,11} It is important to mention that this patient's malaria and dengue infections could have been obtained both in Uganda or Colombia, or 1 in each country, and no good way to know other than timing of travel and symptom onset and possible season/current infection rates.

An active surveillance of vectors, diseases, concurrent infections is necessary, in addition to educational programs, promotion, and prevention campaigns available in VTE.¹⁷ Since it is clear that these AFI's are associated with rainy seasons, poor disposal or disposal of solid waste, stagnant sewage and excrement, as well as lack of drainage facilities, high population density, lack of knowledge of preventive measures.^{3,17} Following up World Health Organization and Pan American Health Organization guidelines will allow a better understanding of the epidemiological trends of concurrent infection in Colombia that will help in a future to design efficient strategies for the control of VTE.^{3,17}

Consent for Publication

No written consent has been obtained from the patients as there is no patient identifiable data included in this case report.

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