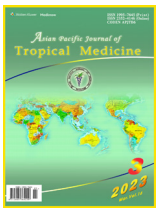

Case Report

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Dengue and *falciparum* malaria co-infection in travelers returning from Burkina Faso: Report of two cases in Northeastern Italy

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ABSTRACT

Rationale: Malaria and dengue are the most prevalent vector-borne diseases in tropical countries. *Plasmodium* parasite and dengue virus (DENV) concurrent infection is possible and often under-recognized in geographical areas where these infections are both endemic.

Patients concern and diagnosis: We describe the first two cases of *Plasmodium falciparum* and DENV-3 co-infection in travelers returning to northeastern Italy from Burkina Faso during 2013-2014.

Interventions: Malaria infection in both patients was treated with mefloquine. Due to the persistence of symptoms despite of the antimalaria treatment, dengue was also investigated; the treatment of dengue was symptomatic.

Outcomes: The patients were discharged in good general condition.

Lessons: The need for surveillance of potential malaria and dengue co-infection in travelers returning to Europe from endemic areas is highlighted, as infection with *Plasmodium* does not exclude arboviral co-infection.

KEYWORDS: Dengue virus; *Falciparum* malaria; Travelers infection; Co-infection; Arbovirus

1. Introduction

International travel has massively increased in the last decades and European physicians are ever more confronted with sick travelers or migrants potentially exposed to various exotic infections. This is a challenge because of the wide differential diagnosis, the non-specific features of most tropical diseases, and the risk of negative outcome for unrecognized severe infections. It is therefore important to be aware of geographic exposure, specific risk profiles and clinical parameters for a correct diagnostic assessment of imported fever.

Malaria and dengue are the two most prevalent arthropod-borne diseases worldwide, major public health concerns in tropical and sub-tropical countries and the most common causes of febrile illness in travelers returning from these countries. The World Health Organization (WHO) estimated that in 2021, malaria caused 247 million clinical episodes compared to 245 million cases in 2020, and estimated number of 593 000 deaths in 2021 compared to 599 000 in 2020[1].

When it comes to dengue virus (DENV) infection, the number of cases reported to WHO increased over 8 fold over the last two decades, and a recent modelling study estimated 390 million infections per year, of which 96 million manifest clinically[2].

Focusing on travel medicine, malaria is diagnosed in 29% of those with fever with a disproportionate higher frequency in travelers returning from Sub-Saharan Africa; this is the most common

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imported infection[3]. Malaria is followed by dengue (15%), which is predominantly found in travelers returning from Southeast Asia, Latin America and the Caribbean[4]. Nevertheless, the true extent of DENV infection amongst travelers is underestimated as many infections are asymptomatic or undiagnosed owing to the non-specific clinical presentation of the disease and lack of familiarity with the disease. Many tropical and sub-tropical countries are endemic for both dengue and malaria; these diseases have similar features and may be clinically indistinguishable. To further complicate the picture, mixed infection can occur.

Here, we present two cases of imported malaria and dengue co-infection in travelers returning to Italy from Burkina Faso. To our knowledge, this is the first report of imported DENV and *Plasmodium (P.) falciparum* malaria co-infection in Italy. Both cases were admitted at the Unit of Infectious Diseases, Morgagni-Pierantoni Hospital in Forlì, northestern Italy.

2. Case report

2.1. Case 1

A 20-year-old Italian woman was admitted to the Infectious Disease Unit, at the "G.B. Morgagni-L.Pierantoni" Hospital, Forlì, Italy, in October 2013 due to a febrile syndrome lasting 7 days associated with diarrhea, itching, and diffuse arthralgia and myalgia. The patient had visited Ougadougouin Burkina Faso between September 14 and October 8, 2013 to participate in an international cooperation project. From the day before her return flight to Italy, she suffered from high fever, diarrhea, abdominal pain, muscle aches, and arthralgia and myalgia of the lower limbs. Once at home, she received treatment with cotrimoxazole, 160 mg trimethoprim/800 mg sulfamethoxazole twice daily and antipyretic drugs [paracetamol, 1 gram (1 000 mg) per dose] for five days by the general practitioner. Because of the persistence of fever with chills (temperature up to 38 ℃), she presented to the Emergency Room.

Medical and surgical history were irrelevant. She denied alcohol or smoking habits, illicit drug use or sexual risk contacts. The patient had been vaccinated against hepatitis A, yellow fever and typhoid fever, while she did not take any malaria prophylaxis during her stay in Burkina Faso. She was taking for some years ethinyl estradiol 0.1 mg + 0.032 mg levonorgestrel.

An ultrasound study of the abdomen and X-ray film of the thorax were performed, but they were negative. No palpable spleen or bowel sounds were preserved. Initial laboratory parameters were as follows: hemoglobin 13.2 g/dL, HTC 39.0% and MCV 78.6 fl, WBC 2 190/μL (with differential N 52.5%, L 36% and M 10%) and platelets 133 000/μL; a mild hyponatremia (serum Na^+ 132 mEq/L) and normal renal function, mild liver cytolysis without hyperbilirubinemia (AST 65 U/L, ALT 72 U/L), LDH 221 U/L, C-reactive protein (CRP) 18.7 mg/dL.

Rapid test for *P. falciparum* malaria was positive and *P. falciparum* trophozoites were observed on peripheral smear with parasitaemia of 0.04%. Treatment with oral mefloquine was started, 750 mg orally as initial dose, followed by 500 mg orally 6 to 12 hours after the initial dose. On the second and third hospital day (Day 8 and 9 of illness), the patient remained febrile and suffered a more intense myalgia with violent spasms of the legs, in addition to increased itching. Laboratory evaluation revealed leukocytes 2 990/μL with differential N 30.8%, L 51.6% and M 11.4%, a mild thrombocytopenia (platelet count: 105 000/μL), CRP 12.6 mg/dL, AST 151 U/L, ALT 165 U/L, LDH 245 U/L. Seventy-two hours after starting treatment with mefloquine, thin and thick smears were tested negative. No hemorrhagic manifestations were present, vital parameters were within normal range and no anemia was documented. Nevertheless, the general conditions of the patient did not improve and the pain in the legs was intense. The combination of clinical data, the results of laboratory tests and epidemiological criteria raised the suspicion of dengue fever. Following an active regional surveillance program to ensure early diagnosis of arbovirus (https://bur.regione.emilia-romagna.it/bur/area-bollettini/bollettini-in-lavorazione/n-105-del-14-04-2022-parte-seconda.2022-04-13.6916747152/approvazione-del-piano-regionale-di-sorveglianza-e-controllo-delle-arbovirosi-anno-2022/allegato-1-piano-regionale-arb.2022-04-13.1649851706), clinical samples were sent to the Regional Reference Centre for Microbiological Emergencies (CRREM) of the Unit of Clinical Microbiology at the Bologna University Hospital, Italy, for the laboratory confirmation. Blood specimens were tested for the presence of IgM and IgG specific antibodies for DENV and chikungunya virus (CHIKV), respectively, by indirect immunofluorescence assay (Euroimmun AG, Lubeck, Germany); for the presence of DENV non-structural protein (NS1) (Platelia Dengue NS1 AG kit, Bio-rad Laboratories, Hercules, CA, USA) and for the presence of CHIKV and DENV RNA in serum and/or plasma samples by using two different real time RT-PCR, as described[4]. While CHIKV serological and molecular tests were negative, DENV non-structural protein (NS1) and DENV RNA in plasma tested positive; as well as anti-DENV specific IgM and IgG. DENV RNA was further characterized and DENV type-3 was identified. The administration of symptomatic treatment with non-steroidal anti-inflammatory drugs and antipyretics led to an improvement of the clinical status. The patient was discharged in good general condition 3 days after the diagnosis of DENV infection.

2.2. Case 2

A 13-year-old child was admitted to "G.B. Morgagni-L.Pierantoni" Hospital (Forlì, Italy) because of a five-day history of high-grade fever, chills and headache, after a 45-day stay in Burkina Faso (June 20 till August 8, 2014). The child, who was previously healthy with no complaints, was initially admitted on August 10, 2014.

Laboratory tests showed no evidence of leukocytosis, while there was a moderate relative neutrophilia (WBC 9 640/μL with differential N 80%, L 12%, M 8%), Hb 14.5 g/dL, HTC 41.3%, MCV 80.2 fl, and platelets 215 000/μL; INR 1.34 (0.80-1.20), alanine aminotransferase (ALT) 25 U/L and CRP 44.7 mg/L (<5.0). Microscopic evaluation of Giemsa-stained thin and thick blood film was suggestive of an infection with *P. falciparum*, with parasitaemia of 1.5%. Serology for viral hepatitis, CHIKV, cytomegalovirus, Epstein-Barr virus, toxoplasmosis and HIV were negative; *Streptococcus pneumoniae* and *Legionella* antigenuria was negative. Computerized tomography of the brain was negative. An X-ray film of the thorax showed the presence of pneumonia at the level of the horn hilar on lower left. An ultrasound of the abdomen was negative, with no signs of hepatosplenomegaly. The child was treated with mefloquine, 15 mg/kg orally as initial dose, followed by 10 mg/kg orally 6 to 12 hours after initial dose, and intravenous amoxicillin/clavulanate, 1 000 mg/200 mg every 8 hours for 5 days, with the resolution of the fever. However, one day after discharge, the child was hospitalized again because of the reappearance of high fever with chills associated with hyperemia of the pharynx, fatigue, arthralgia and myalgia.

The presence of a moderate hypochromic-microcytic anemia was detected (Hb 9.8 g/dL, HTC 27.8%, 76.8 MCV) as well as a relative lymphocytosis (WBC 5 140/μL with differential N 3.6%, L 69.5% with frequent activated lymphocytes, M 14%, B 12.3%), and platelets 172 000/μL; ALT 155 U/L, CRP 17.4 mg/L. Blood cultures were negative and abdomen ultrasound was also negative. The malarial parasitaemia was still positive (0.02% infected red blood cells).

As for case #1, following the surveillance strategies, patient's clinical samples were sent to CRREM laboratory and tested for CHIKV and DENV as described[4].

CHIKV serological and molecular tests gave negative results, while DENV NS1 and DENV RNA tested positive. DENV RNA was further characterized and DENV type-3 was identified. A second blood sample was collected after one week and tested positive for DENV-specific IgG and IgM, thus demonstrating seroconversion. The child received a symptomatic treatment for dengue and an additional anti-malaria treatment with atovaquone and proguanil (Malarone®), 4 tablets a day for three consecutive days. Boluses of methylprednisolone (0.5 mg/kg/day IV/ divided q12 h for three days) were also started, with improvement of clinical status, and hematologic improvement. The *P. falciparum* parasitaemia cleared, with rapid improvement of clinical conditions.

3. Discussion

In Burkina Faso, a Sahelian country in West Africa, the predominant cause of fever has historically been malaria, which transmission is holoendemic. Each year, there are approximately 1.5 million malaria cases and 40 000 deaths. In the last decade, DENV infection has received considerable media attention in this country, as an outbreak of DENV-3 infections was reported in Ouagadougou in 2013[5].

Differential diagnosis between dengue and malaria is complicated in places where they coexist. Presumptive treatment of febrile patients for "malaria" remains the standard care in endemic areas of West Africa given that they share similar clinical findings[6].

Concomitant malaria and DENV infection has become increasingly common in febrile patients returning from the tropics, caused by the overlap of vectors in endemic areas and increased prevalence of dengue fever. Most co-infection cases have been detected in Southern and Southeast Asia while this is a rare event in Europe.

Whether concurrent *Plasmodium*-DENV infection is more severe than single infection is a matter of debate. A recent systematic review and meta-analysis indicated that co-infection with *Plasmodium* and DENV impacted the severity of disease in patients with co-infection, with a significantly higher risk of severe dengue in patients with co-infection than in those with DENV mono-infection[7].

We did not observe an increased severity of the illness due to *P. falciparum* and DENV co-infection in the two index cases that exhibited a benign course of the disease and positive outcome.

Diagnosis of acute DENV infection is mainly performed by detection of IgM[8]; once detectable, anti-DENV IgM may persist in the serum of infected patients for 2-3 months, which would not allow to distinguish between acute and recent infections. In addition, accuracy of IgM serological diagnosis of dengue fever in cases of malaria should be questioned due to concurrent malaria infection, which may cause polyclonal B cell activation[9]. Thus, due to the potential high false-positivity diagnostic tests for IgM and the impossibility to distinguish between acute and recent DENV infection, there may have been an over-estimation of the dengue-malaria co-infection rate in some studies employing serological tests for dengue diagnosis. In our cases, confirmation of DENV infection was obtained by serological tests (NS1 antigen and specific IgM/IgG) paired to molecular methods; the positive detection of viral nucleic acid in plasma samples in both cases confirmed the presence of active DENV infection.

Co-infections are not uncommon and occurrence of mixed infection has different implications for clinicians and public health authorities. In fact, delay in diagnosis of co-infection would lead to deferral of appropriate treatment, which can be devastating, especially in malaria. On the other hand, proper identification of DENV in co-infected travelers returning to Europe from endemic areas is crucial in non-endemic regions where the vector exists, as viremic travelers can introduce DENV into new areas. As a matter of fact, local transmission of DENV in non-endemic areas such as Southern Europe[10] has occurred as the result of new introduction from viremic travelers.

We suggest that DENV and *Plasmodium* infection should be sought simultaneously in individuals who presented with acute febrile illness displaying specific risk profiles including geographic exposure and compatible clinical features, even if one or the other pathogen is positive, as the possibility of mixed infection exists. As dengue fever burden in West Africa is likely obscured by misdiagnosed malaria cases, this African region should also be considered together with Southern Asia, South-East Asia and Latin America as a potential exposure area for malaria-DENV co-infection.

Patients' consent

A signed informed consent for publication was obtained, and the manuscript is in accordance with the regulations of the institution's ethics committee. Ethical approval was not needed by local ethical committee, as this is a case report. Patient provided written informed consent to publish details of this case. A copy of the consent form is available for review by the Editor of this journal.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Authors' contributions

AM and SV: concept and design of study or acquisition of data and analysis and interpretation of data; all authors: drafting the article and revising it critically for important intellectual content; and all authors: final approval of the version to be published.

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