SHORT REPORT: Q FEVER AND PLASMODIUM FALCIPARUM MALARIA CO-INFECTION IN A PATIENT RETURNING FROM THE COMOROS ARCHIPELAGO

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Abstract. Although Plasmodium falciparum malaria and Q fever are both prevalent in Africa, there have been no reports of co-infection to date. We report a case who returned from the Comoros archipelago diagnosed by serologic analysis as well as detection of Coxiella burnetii DNA in acute-phase serum. Thus, Q fever may be associated with malaria infection in travelers returning from disease-endemic countries. This diagnosis should be considered when the response to malaria treatment is incomplete.

The Comoros archipelago is located off the coast of Mozambique in the Indian Ocean. It comprises four different islands that span 1,860 km² with an estimated population in 2002 of 615,000 inhabitants. Three islands, Grande Comore (Ngazidja), Mohéli (Mwali), and Anjouan (Ndzouani), belong to the Federal Islamic Republic, which has been independent since 1975; the island of Mayotte is still a French territory. Although much effort has been put into malaria control, malaria still continues to be a major public health problem in the Comoros, where it represents 15–30% of hospitalizations as well as 15–20% of recorded pediatric deaths. Ninety-five percent of the malaria cases are due to Plasmodium falciparum; up to 59% of the cases are caused by chloroquine-resistant strains. Q fever is caused by the intracellular bacterium Coxiella burnetii and has been described in most parts of the world, including Africa; 5.4% of blood donors in Grande Comore have significant C. burnetii serum antibody titers. The reservoir of C. burnetii is infected mammals, mainly cattle, goats, and sheep. The major route of transmission of Q fever is by aerosol following parturition of an infected animal, but ingestion of unpasteurized milk and milk products is also a risk factor for transmission. All patients with fever returning from disease-endemic areas should be tested for malaria. In contrast, Q fever has rarely been reported as a cause of fever in travelers returning from the tropics; thus routine testing is not normally performed. As part of a prospective study investigating the causes of fever in patients returning from the tropics, we systematically performed serologic analysis for C. burnetii in all patients, including those already diagnosed with malaria. We describe the first case of Q fever and malaria co-infection reported in the literature.

In August 2002, a 29-year-old woman was admitted to the Infectious Disease and Tropical Medicine ward of Northern University Hospital in Marseille, France with fever, headache, vomiting, and myalgia, which occurred three days after returning from a four-week trip to the Comoros. She did not take any malaria prophylaxis and reported contact with cats and goats, as well as consumption of unpasteurized dairy products during her stay. On examination, she had a fever (39°C) and moderate jaundice. Laboratory analysis showed anemia (hemoglobin level = 10.7 g/100 mL), thrombocytopenia (platelet count = 82,000/mm³), normal levels of liver enzymes (alanine aminotransferase = 30 U/L, aspartate aminotransferase = 40 U/L) and an increased level of γ-glutamyl transferase (137 IU/L). Thick and thin blood smears showed a parasitemia of 1% with P. falciparum. She was treated with combination quinine-clindamycin for three days; she defervesced and cleared her parasitemia by day 2. She was subsequently discharged. At follow up on days 7, 14, and 28, thick and thin blood smears remained negative for P. falciparum; there was no evidence of hepatitis. Q fever serologic results were positive with phase I titers of 1:200, 1:25, and 0 for IgG, IgM, and IgA, respectively, as well as phase II titers of 1:400, 1:50, and 1:25 for IgG, IgM, and IgA, respectively. This suggested acute Q fever infection. The patient was asymptomatic and thus was not treated.

Two years later, while analyzing the data from our prospective study of fever in returning travelers, we thawed her acute-phase serum and processed it by a LightCycler PCR assay (Roche, Mannheim, Germany) using hydrolysis probes. Briefly, DNA was extracted with the QIAamp Blood Kit (Qiagen, Hilden, Germany) as described by the manufacturer. Fifty microliters of elution buffer was used to resuspend the DNA. Genomic DNA was stored at 4°C until use in PCR assays. Two different target genes were used in this study: the IS1111 repeated intervening sequence and the IS30a intervening sequence. Primers and hydrolysis probes used in our study are summarized in Table 1. The PCR was performed using a LightCycler apparatus (Roche). The PCR mixture had a final volume of 20 µL and contained 10 µL of the Probe Master kit (Qiagen), 0.5 µL (10 pmol/µL) of each primer, 2 µL (2 µmol/µL) of FAM- and TAMRA-labeled probes, 2 µL of distilled water, and 5 µL of extracted DNA. The amplification conditions were as follows: an initial denaturation step at 95°C for 15 minutes, followed by 40 cycles of denaturation at 95°C for 0 seconds and annealing and elongation at 60°C for 60 seconds, with fluorescence acquisition in single mode. Using this technique, we showed that acute-phase serum of the patient was positive for both target genes with cycle threshold values of 34.8 and 35.9 for the IS1111 and IS30a genes, respectively.

Co-infection with malaria and a second pathogen is rarely reported in travelers. This is mainly because malaria represents more than 60% of fevers in exposed travelers; additionally, malaria is easier to diagnose than many other infectious diseases. Consequently, other infections are not suspected un-
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TABLE 1

Primer and probes used to detect Coxiella burnetii in the acute phase sera from the patient

<table>
<thead>
<tr>
<th>Primer/Cbis30aR</th>
<th>Probe/Cbis30aF</th>
<th>Length of the expected PCR product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primer IS1111F</td>
<td>Probe IS1111</td>
<td>Length of the expected PCR product IS1111 = 200 bp</td>
</tr>
<tr>
<td>Primer IS1111R</td>
<td>Probe IS1111</td>
<td>Length of the expected PCR product IS1111 = 120 bp</td>
</tr>
</tbody>
</table>

*bp = basepairs.

less patients remain symptomatic after treatment for malaria. Because many other infectious diseases may be asymptomatic or pauci-symptomatic or even have spontaneous resolution, the second infection remains undiagnosed unless patients are routinely screened. Co-infection with malaria has been reported with dengue, leptospirosis, non-typhoidal Salmonella bacteremia, and human immunodeficiency virus (HIV). Co-infection with C. burnetii and spotted fever group rickettioses or tularemia has also been reported.[14] To our knowledge, C. burnetii co-infection with malaria has never been reported. The overlapping geographic distribution of malaria and Q fever in the Comoros suggests that simultaneous infection may occur.[3] The presence of antibodies to C. burnetii in humans has been reported in most of the malaria-endemic countries in Africa, including Mauritania.[15] Zambias. Angola, Burkina Faso, Democratic Republic of Congo, Central African Republic, Mali, Ivory Coast, and the Federal Islamic Republic.[3] Interestingly, the presence of antibodies to C. burnetii correlates with the prevalence of cattle breeding; some countries, including Mali, Burkina Faso, and Mauritania, have a prevalence of antibody to C. burnetii that exceeds 30%.[3,15]

The Federal Islamic Republic is one of the world’s poorest countries, with a young and rapidly growing population and few natural resources. Agriculture (including fishing, hunting, and forestry), contributes 40% to the gross domestic product, employs 80% of the labor force, and provides most of the exports such as vanilla, cloves, perfume essences, copra, coconuts, bananas, and cassava (tapioca). There is no large-scale cattle breeding in Federal Islamic Republic, but families generally have one or two domestic animals such as goats or sheep. Consequently, as reported for this case, contact with goats and sheep is a common risk factor for infection. In a reported Q fever outbreak that occurred during a safari trip in Kenya, the only risk factor associated with Q fever was a visit to a shack where patients had contact with local goats.[6] Cats have also been suggested as source of Q fever. In South Africa and Zimbabwe, respectively, 2% and 13% of cats tested for antibodies to C. burnetii were positive, suggesting that they might be a source of transmission to humans.[17] Similarly, 8.3% and 11.6% of dogs from Côte d’Ivoire and Senegal, respectively, had antibodies to C. burnetii.[18] Serologic cross-reactions during malaria infection have been reported with concomitant HIV or schistosomal infections, but this is a poorly understood phenomenon.[19] This indicates that culture and molecular diagnostics, especially PCR of whole blood or, as reported here, acute-phase serum, is mandatory in confirming true co-infection. In our case, the diagnosis of C. burnetii infection was supported both by serologic analysis and PCR amplification of two genes specific for C. burnetii.[20] Due to the high prevalence of malaria and other infectious diseases such as dengue, Q fever, and salmonellosis in some tropical countries, co-infection may occur in significant numbers of travelers returning from these areas. Despite the fact that most cases are asymptomatic, C. burnetii infection should be suspected when the clinical response to anti-malarial therapy is incomplete.

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