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False-positive rapid diagnostic test for malaria in new world cutaneous leishmaniasis: a tale of two travelers

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***Abstract*:** We report two immigrants from Cuba seen in a US travel clinic with a confirmed diagnosis of cutaneous leishmaniasis in whom we also suspected malaria co-infection. Both individuals likely acquired leishmaniasis in the Darien Gap region of Panama during their migratory path to the United States. As part of their clinical workup to rule out malaria, a rapid malaria antigen testing for *P. falciparum* was obtained and reported positive in both patients, However, both a qualitative reverse transcription-polymerase chain reaction (RT-PCR) for *Plasmodium falciparum* in blood and repeated thick-and-thin smear direct microscopy were negative in both, deeming the rapid malaria test as a false-positive. Thus, confirmation of malaria in travelers requires thick-and-thin film microscopy. Clinicians should be aware of the growing recognition of the possibility of false-positive malaria rapid diagnostic tests in those with some forms of leishmaniasis

Keywords: cross-reactivity, cutaneous leishmaniasis, leishmaniasis, malaria, *Plasmodium falciparum*

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Introduction

Cutaneous leishmaniasis is a major neglected tropical disease (NTDs), endemic in over 98 countries and an estimated 350 million people are at risk.[1] Different subspecies can cause diverse clinical manifestations. In the Americas (New World), most cases are caused by infection with *Leishmania mexicana* species complex, *Leishmania amazonensis*, and the *Leishmania Viannia* subgenus complex.[2] Infection with *Leishmania panamensis* manifests as either cutaneous leishmaniasis, diffuse cutaneous leishmaniasis, or cutaneous leishmaniasis with early mucosal involvement.[3] Neglected tropical diseases do not occur in isolation: at-risk individuals may have concomitant NTDs co-infections and may be poly parasitized.[4] For example, a recent study from Southern Ghana demonstrated a high prevalence of *Plasmodium falciparum* and *Schistosoma mansoni* infection.[5]

Case descriptions

Case 1

A 24-year-old Cuban immigrant came in with worsening nonhealing lower extremity ulcers despite oral antibiotic therapy and wound care. The patient reported these lesions gradually grew with subsequent ulceration over the course of 1 to 2 months. He recently arrived at the U.S. seeking asylum. He first noticed them while traveling in the jungle between Panama and Colombia (Darien Gap region). On exam, the ulcerative lesion measured 4 cm on the dorsum of the right foot. We identified a second 3.5 cm ulcer on the lower anterior shin (Figure 1). There was no evidence of mucosal or visceral involvement on initial physical exam.

Case 2

A 47-year-old man who was a traveling companion of the patient described above presented with

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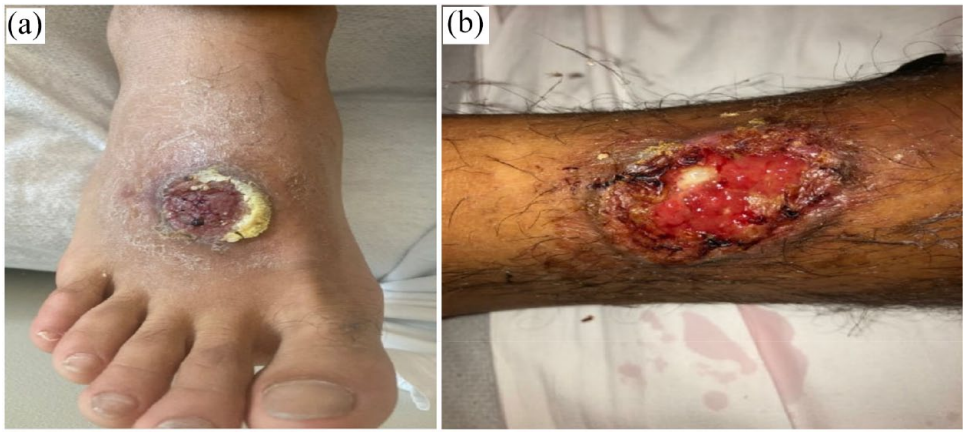

Figure 1. Case 1 lower extremities lesions: (a) Right Foot and (b) Left Shin.

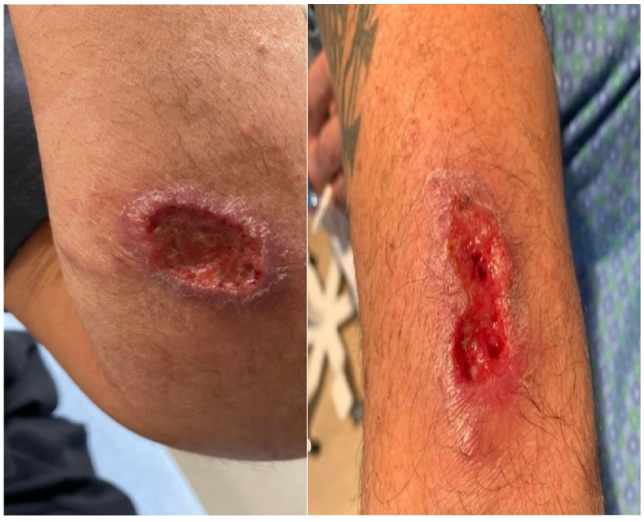

Figure 2. Case no.2 left upper extremity lesions.

a total of 10 lesions on bilateral upper (Figure 2) and lower extremities and flank, all >1 cm with the largest measuring 5 cm. Tissue samples were sent to the Centers for Disease Control and Prevention, Atlanta, GA, USA, for confirmation of diagnosis. Samples from our two patients were positive for *Leishmaniasis* by immunohistochemistry and histopathologic evidence of amastigotes in both cases. Both received an initial 3-day course of liposomal amphotericin B (Ambisome©) followed by miltefosine (Impavido©). They were treated with a total 28-day course of miltefosine with eventual resolution of lesions. As part of their clinical workup to rule out malaria, a rapid malaria antigen testing for *P falciparum* was obtained and reported positive in both patients (BinaxNOW malaria, Abbott Laboratories, Elk Grove Village, IL, USA). However, both a qualitative RT-PCR for *P falciparum* in blood (ARUP Laboratories, Salt Lake City, UT, USA) and repeated thick-and-thin smear direct microscopy were negative in both patients.

Discussion

We report two Cuban travelers seen in a US travel clinic with a confirmed diagnosis of cutaneous leishmaniasis in whom we also suspected malaria co-infection. The diagnosis of leishmaniasis in both of our patients was made in both patients by immunohistochemical confirmation and by visualization of amastigotes in biopsies of cutaneous lesions. Both individuals likely acquired leishmaniasis in the Darien Gap region of Panama during their migration to the United States. As part of their workup to detect other potential tropical infections, we obtained rapid malaria diagnostic tests (RDTs) in both patients. Both patients had positive RDTs for *P falciparum* but no evidence of parasites

Malaria rapid diagnostic tests to detect *P falciparum* utilize histidine-rich protein 2 (PfHRP2) and pan, *P falciparum* or *P vivax*–specific *Plasmodium* lactate dehydrogenase to differentiate *P falciparum* from non–*P falciparum* infections. Obtaining RDTs provide initial information that assist clinicians in starting empiric malaria therapy. However, it is important to consider that the diagnostic value of these tests is compromised by the occurrence of false-positive results that require

confirmation with direct microscopy of peripheral blood smears. There are a few conditions to consider that may produce false-positive RDTs. For example, patients with detectable rheumatoid factor may have false-positive malaria RDT.[6] In addition, false-positive malaria RDT results have also been reported in persons with Human African Trypanosomiasis (HAT),[7] acute schistosomiasis,[8] and more recently in a returning traveler with enteric fever due to *Salmonella typhi*.[9] False-positive reports have been documented, specifically for the *P falciparum* band on the rapid malarial antigen test in patients with positive *Leishmania* seropositivity.[6] Conversely, cross-reactivity between *Plasmodium* and leishmaniasis has been observed with false-positive leishmaniasis antigens by immunofluorescent antibody (IFA) testing, in patients with malaria.[6,10] Interestingly, there are no documented antigens shared between *Plasmodium* and *Leishmania* spp.,[10] so this relationship is poorly understood.

Conclusions

Clinicians should be aware of the growing recognition of the possibility of false-positive malaria rapid diagnostic tests in those with some forms of leishmaniasis, as well as other NTDs such as HAT and schistosomiasis. This consideration is particularly important for tropical regions of the world where there is no quality-assured microscopy available to confirm malaria diagnosis. In other settings, the use of rapid diagnostic tests may assist clinicians in initiation early therapy. However, quality-assured examination by direct microscopy of blood smears to detect *Plasmodium* parasites need to be performed as it is the gold standard for confirming a diagnosis of malaria.

Consent for publication

Verbal informed consent for publication was obtained from both patients.

Author contribution(s)

Rebecca Unterborn: Investigation; Writing – original draft.

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