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BRIEF REPORT

# African Tick Bite Fever Treated Successfully With Rifampin in a Patient With Doxycycline Intolerance

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African tick bite fever is the most commonly encountered travel-associated rickettsiosis, occurring in as many as 5% of travelers returning from rural subequatorial Africa. This case report illustrates that rifampin represents an effective alternative to doxycycline for treatment of African tick bite fever in some selective situations.

**Keywords.** *Rickettsia africae*; African tick bite fever; rifampin.

Rickettsiae are obligate intracellular bacteria that cause a wide range of zoonotic diseases worldwide. *Rickettsia africae*, the causative agent of African tick bite fever (ATBF), typically causes a self-limited, acute febrile illness, but can occasionally lead to severe complications including subacute neuropathy [1], myocarditis [2], acute neuropsychiatric symptoms [3], reactive arthritis, and prolonged fevers [4]. Doxycycline is the treatment of choice for all rickettsial diseases and effectively reduces symptom duration and complications; nonetheless, a small percentage of patients cannot receive tetracycline-class antibiotics because of intolerance to these drugs [5–7]. Here we present a case of a patient with ATBF and intolerance to doxycycline who had a rapid and complete response following therapy with rifampin.

## CASE PRESENTATION

A 53-year-old immunocompetent white male with a history of doxycycline intolerance presented with 4-day history of a new skin lesion, myalgia, and generalized malaise. These symptoms started about 9 days after being on a safari in the Hluhluwe region of KwaZulu-Natal, South Africa. During this time, he was compliant with antimalarial prophylaxis (atovaquone/proguanil), and used insect repellant. The patient did not recall any tick bites. Prior to his trip, he had visited a travel clinic and was current on all of his vaccines. His doxycycline intolerance consisted of blistering and ulcerated oral lesions in the corner of his mouth as well as between digits of his hands within hours of exposure of a 100-mg oral dose of this drug administered for the treatment of rosacea. This reaction also occurred when a lower dosage (40 mg daily) was administered.

When seen in the clinic he appeared to be generally well, with stable vital signs, and was afebrile. Physical examination was remarkable for tender firm lymph nodes in the inguinal and right popliteal region and a 1-cm pustular tender nodule with surrounding erythema and induration in his right popliteal fossa (Figure 1), but no rash was present. A presumptive diagnosis of ATBF was made. Because of the patient's history of doxycycline intolerance and overall clinical stability, no initial treatment was prescribed. A punch biopsy was performed on the nodule, which was sent to the Centers for Disease Control and Prevention for diagnostic testing. However, 36 hours later the patient developed fever to 38.3°C and headache. A real-time polymerase chain reaction (PCR) assay targeting a segment of the 23S ribosomal RNA gene of *Rickettsia* species [8] was performed on DNA extracted from a portion of the skin biopsy specimen and confirmed a rickettsial infection. The patient was started on rifampin 450 mg twice a day. Within 12 hours of starting therapy, his temperature returned to normal and his condition improved considerably with resolution of his headache and myalgia. The patient completed a 10-day course of rifampin with complete resolution of symptoms. *Rickettsia africae* was subsequently isolated in Vero E6 cells after 10 days. A nested PCR assay amplified a 532-bp segment of the *sca*0 (*omp*A) gene [9, 10], and sequencing of this amplicon revealed 100% identity with the corresponding sequence of *R. africae*. A convalescent serum sample collected approximately 5 weeks after recovery revealed a reciprocal immunoglobulin antibody titer to *R. africae* of 2048.

## DISCUSSION

Standard therapy for adult patients with ATBF is doxycycline 100 mg twice daily [11]. Alternatives to doxycycline for the treatment of ATBF are limited. Chloramphenicol is identified as an alternative drug, but oral formulations are not currently available in the United States [12, 13]. Ciprofloxacin [4, 5, 12] and some macrolides, including azithromycin and erythromycin [14, 15], have been used alone or in combination with other antibiotics as treatment of suspected ATBF, although the efficacy of these antibiotics against *R. africae* is inconclusive. Josamycin, another macrolide, has been recommended for

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**Figure 1.** Pustular lesion with surrounding erythema and induration in the right popliteal fossa.

treatment of ATBF in pregnant women based on in vitro sensitivity [12, 16], but clinical data are lacking.

In the current case report, we document a patient with culture-confirmed ATBF who was successfully treated with rifampin. Although rifampin is not considered a first-line treatment for any rickettsial infection, it has been used successfully as monotherapy to treat pregnant women and children infected with *Anaplasma phagocytophilum* [17–19]. We opted to treat this patient with rifampin because of his inability to take doxycycline, and because most *Rickettsia* species, including *R. africae*, are highly susceptible to rifampin in vitro [16, 20]. A few case reports describe the use of rifampin in combination with erythromycin or azithromycin to successfully treat Mediterranean spotted fever [21] and ATBF [22], but there are no reports of its successful use as monotherapy for ATBF. Our patient's prompt response to rifampin suggests that its use may be considered in specific clinical situations when doxycycline is contraindicated. Some other pathogenic *Rickettsia* species endemic to sub-Saharan Africa, including *Rickettsia conorii* and *Rickettsia sibirica mongolotimonae* [23], are also susceptible to rifampin in vitro [16].

Rifampin resistance occurs in several bacteria, including *Staphylococcus aureus* [24], *Neisseria meningitidis* [25], *Mycobacterium tuberculosis* [26], *Escherichia coli* [27, 28], and *Streptococcus pneumoniae* [29]. In addition, a few pathogenic species of spotted fever group *Rickettsia*, including *Rickettsia massiliae* and *Rickettsia aeschlimannii*, are resistant to rifampin in vitro [16, 30], and therapeutic failures have been reported when rifampin is used as primary therapy for rickettsial infections in regions where *R. massiliae* is prevalent [31, 32]. Finally, because *R. massiliae* and *R. aeschlimannii* cause disease manifestations similar to *R. africae*, and occur sympatrically with *R. africae* in some areas of Africa [23], rifampin should not be considered as first-line therapy for all patients returning from Africa with fever and an eschar, but reserved only for specialized situations such as PCR-confirmed infections with rifampin-susceptible rickettsial pathogens as described in this report.

## CONCLUSIONS

ATBF is the most commonly encountered travel-associated rickettsiosis, occurring in as many as 5% of travelers returning from rural subequatorial Africa [4, 33]. Physicians should consider this infection in patients who present with compatible signs and symptoms and a travel history to a region where *R. africae* is endemic. Treatment is generally empiric because accurate diagnostic assays are largely retrospective and of limited availability. This case report illustrates that rifampin represents an effective alternative to doxycycline for treatment of ATBF in some selective situations.

## Notes

***Disclaimer.*** The findings and conclusions are those of the authors and do not necessarily reflect the views of the US Department of Health and Human Services.

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