Infect Chemother. 2022 Mar;54(1):202-207
https://doi.org/10.3947/ic.2019.0073
pISSN 2093-2340·eISSN 2092-6448

Infection & Chemotherapy

Case Report

Check for updates

A Case of African Tick-Bite Fever in a Returning Traveler from Southern Africa

Woonji Lee [1], Hye Seong [1], Jung Ho Kim [1], Heun Choi [1], Jun Hyoung Kim [1], Jin Young Ahn [1], Su Jin Jeong [1], Nam Su Ku [1], Jun Yong Choi [1], Choon-Mee Kim [2], Dong-Min Kim [3], and Joon-sup Yeom [1]

[1]Division of Infectious Disease, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
[2]Premedical Science, Chosun University College of Medicine, Gwangju, Korea
[3]Division of Infectious Disease, Department of Internal Medicine, Chosun University College of Medicine, Gwangju, Korea

Received: Nov 19, 2019
Accepted: Dec 30, 2019
Published online: Jul 13, 2020

Corresponding Author:
Joon-sup Yeom, MD, PhD
Division of Infectious disease, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel: +82-10-5417-2877
Fax: +82-2-393-6884
Email: JOONSUP.YEOM@yuhs.ac

ORCID iDs
Woonji Lee
https://orcid.org/0000-0002-3431-3633
Hye Seong
https://orcid.org/0000-0002-5633-7214
Jung Ho Kim
https://orcid.org/0000-0002-5033-3482
Heun Choi
https://orcid.org/0000-0002-9622-9381
Jun Hyoung Kim
https://orcid.org/0000-0002-0595-2110
Jin Young Ahn
https://orcid.org/0000-0002-3740-2826

ABSTRACT

African tick-bite fever (ATBF), caused by *Rickettsia africae*, is the second most frequent cause of fever after malaria in travelers returning from Southern Africa. As the Korean outbound travelers are increasing every year, tick-borne rickettsial diseases as a cause of febrile illness are likely to increase. We describe a febrile Korean returning traveler who showed two eschars after visiting the rural field in Manzini, Swaziland. We performed nested polymerase chain reaction using the eschar and diagnosed the patient with ATBF. He was treated with oral doxycycline for 7 days, and recovered without any complications. We believe that the present case is the first ATBF case diagnosed in a Korean traveler.

Keywords: *Rickettsia africae*; African tick-bite fever; Spotted fever group rickettsiosis; Polymerase chain reaction

INTRODUCTION

Recently, rickettsioses have become important in the field of travel medicine, as increasing number of travelers are being exposed [1]. According to GeoSentinel surveillance network from 1996 to 2008, rickettsial diseases have been reported in 280 returning international travelers. Among these travelers, 231 individuals had spotted fever group (SFG) rickettsioses [2]. African tick-bite fever (ATBF) is one of the tick-borne SFG rickettsioses caused by *Rickettsia africae*. It is the second most frequent cause of fever after malaria in travelers returning from Southern Africa [3]. As Korean outbound travelers are increasing every year, tick-borne rickettsial diseases are likely to increase in returning Korean travelers. In the present report, we describe a case of ATBF in a traveler returning from Manzini, Swaziland in Southern Africa.

CASE REPORT

A 36-year-old man had fever (38.4°C) for 5 days after the day of returning from Manzini, Swaziland. He visited Manzini for 15 days to take a picture of children on the rural field in early March 2018.

ic Infection & Chemotherapy

Su Jin Jeong
https://orcid.org/0000-0003-4025-4542
Nam Su Ku
https://orcid.org/0000-0002-9717-4327
Jun Yong Choi
https://orcid.org/0000-0002-2775-3315
Choon-Mee Kim
https://orcid.org/0000-0003-4404-6214
Dong-Min Kim
https://orcid.org/0000-0001-6373-0922
Joon-sup Yeom
https://orcid.org/0000-0001-8940-7170

Funding
None.

Ethics statement
The study was reviewed and approved by the IRB (No. 4-2020-0012) in Human Research Protection Center of Severance Hospital Yonsei University. We got the concent to use the photographs of patient's skin lesion.

Conflict of Interest
No conflicts of interest.

Author Contributions
Conceptualization: JSY. Data curation: WJL. Methodology: DMK, CMK. Supervision: JSY, DMK. Visualization: WJL. Writing - original draft: WJL. Writing - review & editing: WJL, JSY, DMK, HS, JHK, JHK, HC, JYA, SJJ, NSK, JYC.

The patient had general weakness, myalgia, night sweats, and sore throat. Physical examination revealed two eschars on the abdominal skin and the left posterior thigh (**Fig. 1**). No generalized skin rash was observed. His bilateral inguinal lymph nodes were enlarged. On the first day at the clinic, laboratory tests revealed slightly decreased white blood cell count (3,600/mm^3 with 65.6% polymorphonuclear cells and 22.7% lymphocytes) and elevated C-reactive protein (22.6 mg/L). Hemoglobin was 14.5 g/dL, and the platelet count was 198 x 10^3/mm^3. Chemistry examination of the patient was normal with a blood urea nitrogen of 7.3 mg/dL, and creatinine of 0.75 mg/dL. His liver function tests were normal with aspartate aminotransferase level of 29 IU/L and alanine aminotransferase level of 20 IU/L. Blood cultures, malaria microscopy, and rapid antigen test were negative. Serology was negative for *Orientia tsutsugamushi*.

Since infections caused by tick-borne bacteria, including rickettsioses, were suspected due to the presence of eschars, nested polymerase chain reaction (PCR) for *Rickettsia, Anaplasma,* and *Ehrlichia* was done using blood and the eschars removed from the patient's skin on the day after the administration of antibiotics. We performed nested PCR using *rOmpA* [4], and *gltA* genes [5], and real-time PCR assays for panrickettsia (PanR8) [6] to detect *Rickettsia* spp., and *groEL* gene was used for detecting *Anaplasma* and *Ehrlichia* [7]. For the blood sample, PCR of the buffy coat was negative for *Rickettsia* spp., *Anaplasma* and *Ehrlichia*. For the eschar on the thigh, nested PCR was negative for *Anaplasma* and *Ehrlichia*.

We analyzed the eschar using a primer based on the nucleotide sequences of a gene encoding the 17 kDa antigen [8] of *R. africae* (**Fig. 2**). Primers Rr17k.1p (5′-TTT ACA AAA TTC TAA AAA CCAT-3′) and Rr17k.539n (5′-TCA ATT CAC AAC TTG CCA TT-3′) were used for the first PCR, and nested PCR primers Rr17k.90p (5′-GCT CTT GCA ACT TCT ATG TT-3′) and Rr17k.539n (5′-TCA ATT CAC AAC TTG CCA TT-3′) were used to amplify a 423-bp fragment. The strains which were used as positive controls in this study was *Rickettsia conorii*. Distilled water was used as the negative control. The nested PCR product by the primer based on the 17 kDa antigen of *R. africae* was positive, and it was a 99.8% match with the complete genome of *R. africae* strain ESF-5.

The patient was treated with oral doxycycline 100 mg every 12 hours for 7 days. He recovered well without any complications.

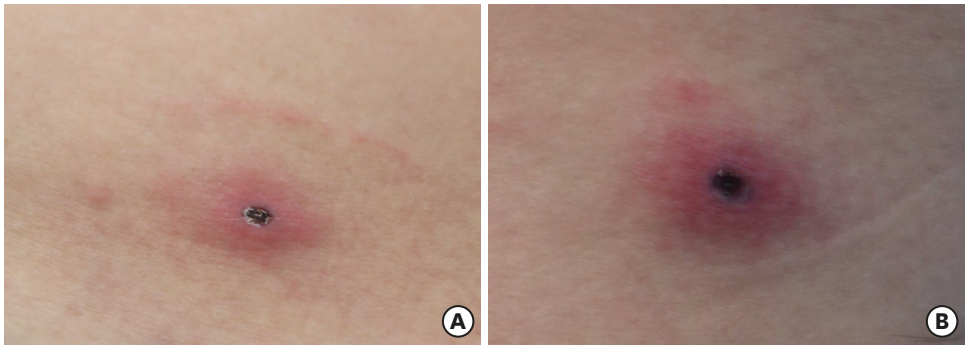

Figure 1. Two eschars were observed on the abdomen (A) and the left posterior thigh (B).

https://doi.org/10.3947/ic.2019.0073

ic Infection & Chemotherapy

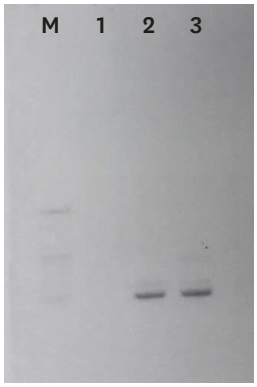

Figure 2. Agarose gel electrophoresis of the amplified DNA fragments.
The DNA fragments were obtained by nested polymerase chain reaction (PCR) of the eschar using a primer based on nucleotide sequences of a gene encoding the 17 kDa antigen of *Rickettsia africae*. A 423-bp DNA fragment was amplified by nested PCR.
M, Marker; 1, negative control; 2, positive control; 3, eschar of thigh.

DISCUSSION

We believe that the present case is the first ATBF case diagnosed in a Korean traveler, and the second imported rickettsial infection [9]. African tick-bite fever is one of the tick-borne SFG rickettsioses and is caused by *R. africae.* Many molecular assays from humans, ticks and mites demonstrate that various SFG rickettsioses such as *R. japonica, R. conorii, R.akari* are prevalent in Korea [10], but *R. africae* acquired in Korea has not been reported.

R. africae is an obligate intracellular Gram-negative rod bacterium, which was first isolated in 1990. It is transmitted by the bite of the tick of genus *Amblyomma*, which is a parasite of cattle and wild ungulates and a vector and reservoir of *R. africae*. In particular, *Amblyomma hebraeum* are found primarily in Southern Africa and *Amblyomma variegatum* are abundantly found in western, central, and eastern Africa. Infection rates are remarkably high and as many as 100% of the *Amblyomma* could be infected with *R. africae* [11]. Up to 54% of the patients with ATBF have multiple and clustered eschars, a finding that indicates aggressive biting habits and attacking characteristics of the *Amblyomma* [12].

Until 2004, more than 350 travel-associated cases of ATBF have been reported from South Africa, Europe, North America, Australia, Argentina, and Japan. Most of the patients were infected in South Africa, where many popular wildlife attractions are endemic for *R. africae* infection [13]. In the past 10 years, more than 100 cases of ATBF have been reported. All of these patients had traveled to Southern Africa and 81% (86/106) of these travelers stayed in South Africa. Other visited countries included Swaziland (2.8%), Zimbabwe (2.8%), Botswana and Malawi (1.8%), and Namibia, Zambia, Ethiopia, and Gambia (0.9%) [1]. Traveling for game hunting, trip to southern Africa, and traveling during the rainy summer from November through April have been identified as risk factors for ATBF [14].

Time lag from the tick bite to the onset of symptoms is usually 5 - 7 days or it can be as long as 10 days. Eschars are predominantly localized in the lower limbs as observed in the present case [3]. Along with eschars, common clinical features include flue like symptoms such as fever, myalgia, fatigue, and headache. Regional lymphadenitis and generalized skin rash is commonly found [1]. ATBF is usually a benign disease compared to Mediterranean spotted

https://doi.org/10.3947/ic.2019.0073

fever caused by *Rickettsia conorii* which is also frequently found in Southern Africa. However, there is a possibility of complications such as neuropsychiatric symptoms, encephalopathy, peripheral neuropathy [3], retinitis, or myocarditis [1] if left untreated. Hematologic and biochemical parameters during acute phase of ATBF showed mild abnormalities such as lymphopenia and increased C-reactive protein [15].

Usually, rickettsioses are diagnosed by epidemiological data and clinical features, but typical signs might be absent or might remain unnoticed [1]. There are no rapid confirmatory assays for *R. africae*. Hence, the therapeutic interventions are based on clinical suspicion of ATBF [3]. For microbiological diagnosis, detection of *R. africae* antigen could be done by immunohistochemistry using monoclonal antibodies or PCR using blood or eschar [1]. Seroconversion may occur more than 3 weeks after the onset of symptoms and cross-reactivity can be seen with other SFG rickettsioses. For example, the Korea Centers for Disease Control and Prevention can perform serodiagnosis of SFG rickettsiosis using *R. japonica*, which may have cross-reactivity with *R.africae*. Moreover, seroconversion with both IgG and IgM may not occur when doxycycline is administered in the first week of the clinical course of ATBF [16]. Therefore, the diagnosis is made by PCR [3], and the eschar should be the preferred source of genomic detection rather than blood. Because *Rickettsiae* multiply at the site of inoculation, and the use of skin biopsy or eschar samples improves sensitivity for SFG rickettsiosis assays (67%) compared to blood samples (42%) [17]. In this case, nested and real-time PCR tests of blood samples for Rickettsia spp. were negative. This result is largely because we obtained the blood samples 10 days after symptoms have developed. Nucleic acid amplification tests using blood are more sensitive in acute illness such as febrile phase ideally days 1 to 5 of illness [18]. Considering *R. africae*, the genes encoding the 16S rRNA and outer membrane proteins *rOmpA*, *rOmpB*, and *PS120* are used in the PCR [19]. In this study, we used partial 17 kDa antigen gene encoded for the *Rickettsia* genus-specific 17 kDa outer membrane protein to screen the DNA presence using nested PCR [8].

Once ATBF is suspected, treatment should be initiated promptly before microbiological confirmation[20]. Doxycycline 200 mg daily should be started for a duration of 7 days in adults and children aged more than 8 years. Macrolides such as clarithromycin and azithromycin might be alternatives for adults who are allergic to tetracycline or for children aged less than 8 years [3].

We reported a case of ATBF caused by *R. africae* in a patient returning from Manzini, Swaziland in Southern Africa. Tick-borne SFG rickettsioses, especially ATBF, should be considered by the physicians in travelers returning from Southern Africa with suspected clinical features such as fever or eschars. Since commercialized diagnostic tests are not available in South Korea, clinical suspicion is important for prompt initiation of antibiotics to reduce the complications.

ACKNOWLEDGEMENTS

First of all, we would like to thank Dong-Min Kim at the Chosun University College of Medicine for performing polymerase chain reactions and detection of *R.africae*. We thank Soo-Min Kim in the Department of Dermatology, Yonsei University College of Medicine for obtaining eschars and taking photographs of the patient.

REFERENCES

1. Delord M, Socolovschi C, Parola P. Rickettsioses and Q fever in travelers (2004-2013). Travel Med Infect Dis 2014;12:443-58.
PUBMED | CROSSREF
2. Jensenius M, Davis X, von Sonnenburg F, Schwartz E, Keystone JS, Leder K, Lopéz-Véléz R, Caumes E, Cramer JP, Chen L, Parola P; GeoSentinel Surveillance Network. Multicenter GeoSentinel analysis of rickettsial diseases in international travelers, 1996-2008. Emerg Infect Dis 2009;15:1791-8.
PUBMED | CROSSREF
3. Eldin C, Parola P. Update on tick-borne bacterial diseases in travelers. Curr Infect Dis Rep 2018;20:17.
PUBMED | CROSSREF
4. Eremeeva ME, Bosserman EA, Demma LJ, Zambrano ML, Blau DM, Dasch GA. Isolation and identification of Rickettsia massiliae from Rhipicephalus sanguineus ticks collected in Arizona. Appl Environ Microbiol 2006;72:5569-77.
PUBMED | CROSSREF
5. Jado I, Oteo JA, Aldámiz M, Gil H, Escudero R, Ibarra V, Portu J, Portillo A, Lezaun MJ, García-Amil C, Rodríguez-Moreno I, Anda P. Rickettsia monacensis and human disease, Spain. Emerg Infect Dis 2007;13:1405-7.
PUBMED | CROSSREF
6. Kato CY, Chung IH, Robinson LK, Austin AL, Dasch GA, Massung RF. Assessment of real-time PCR assay for detection of Rickettsia spp. and Rickettsia rickettsii in banked clinical samples. J Clin Microbiol 2013;51:314-7.
PUBMED | CROSSREF
7. Wei F, Song M, Liu H, Wang B, Wang S, Wang Z, Ma H, Li Z, Zeng Z, Qian J, Liu Q. Molecular detection and characterization of zoonotic and veterinary pathogens in ticks from Northeastern China. Front Microbiol 2016;7:1913.
PUBMED | CROSSREF
8. Noh Y, Lee YS, Kim HC, Chong ST, Klein TA, Jiang J, Richards AL, Lee HK, Kim SY. Molecular detection of Rickettsia species in ticks collected from the southwestern provinces of the Republic of Korea. Parasit Vectors 2017;10:20.
PUBMED | CROSSREF
9. Kim KH, Kim NH, Kim M, Kim CJ, Jeon JH, Park WB, Jang WJ, Park SW, Kim IS, Oh MD, Choe KW. A case of tsutsugamushi disease after traveling to the Philippines. Infect Chemother 2008;40:333-6.
CROSSREF
10. Kim YS, Choi YJ, Lee KM, Ahn KJ, Kim HC, Klein T, Jiang J, Richards A, Park KH, Jang WJ. First isolation of Rickettsia monacensis from a patient in South Korea. Microbiol Immunol 2017;61:258-63.
PUBMED | CROSSREF
11. Parola P, Paddock CD, Raoult D. Tick-borne rickettsioses around the world: emerging diseases challenging old concepts. Clin Microbiol Rev 2005;18:719-56.
PUBMED | CROSSREF
12. Norval RA, Andrew HR, Yunker CE. Pheromone-mediation of host-selection in bont ticks (Amblyomma hebraeum koch). Science 1989;243:364-5.
PUBMED | CROSSREF
13. Jensenius M, Fournier PE, Raoult D. Tick-borne rickettsioses in international travellers. Int J Infect Dis 2004;8:139-46.
PUBMED | CROSSREF
14. Jensenius M, Fournier PE, Vene S, Hoel T, Hasle G, Henriksen AZ, Hellum KB, Raoult D, Myrvang B; Norwegian African Tick Bite Fever Study Group. African tick bite fever in travelers to rural sub-Equatorial Africa. Clin Infect Dis 2003;36:1411-7.
PUBMED | CROSSREF
15. Jensenius M, Fournier PE, Hellum KB, Wesslén L, Caruso G, Priø T, Løhne K, Vene S, Raoult D, Myrvang B. Sequential changes in hematologic and biochemical parameters in African tick bite fever. Clin Microbiol Infect 2003;9:678-83.
PUBMED | CROSSREF
16. Fournier PE, Jensenius M, Laferl H, Vene S, Raoult D. Kinetics of antibody responses in Rickettsia africae and *Rickettsia conorii* infections. Clin Diagn Lab Immunol 2002;9:324-8.
PUBMED

https://doi.org/10.3947/ic.2019.0073

ic Infection & Chemotherapy

17. Paris DH, Dumler JS. State of the art of diagnosis of rickettsial diseases: the use of blood specimens for diagnosis of scrub typhus, spotted fever group rickettsiosis, and murine typhus. Curr Opin Infect Dis 2016;29:433-9.
PUBMED | CROSSREF

18. Abdad MY, Abou Abdallah R, Fournier PE, Stenos J, Vasoo S. A concise review of the epidemiology and diagnostics of Rickettsioses: Rickettsia and Orientia spp. J Clin Microbiol 2018;56:e01728-17.
PUBMED | CROSSREF

19. Jensenius M, Fournier PE, Kelly P, Myrvang B, Raoult D. African tick bite fever. Lancet Infect Dis 2003;3:557-64.
PUBMED | CROSSREF

20. Botelho-Nevers E, Socolovschi C, Raoult D, Parola P. Treatment of Rickettsia spp. infections: a review. Expert Rev Anti Infect Ther 2012;10:1425-37.
PUBMED | CROSSREF

https://doi.org/10.3947/ic.2019.0073