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【 CASE REPORT 】

Imported African Tick Bite Fever in Japan: A Literature Review and Report of Three Cases

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Abstract:
African tick bite fever (ATBF) is an acute febrile illness caused by *Rickettsia africae*. ATBF is an important differential diagnosis of acute febrile illness among returned travelers. However, little information is available on ATBF cases imported to Japan, as only seven have been reported to date. To characterize the epidemiological and clinical profiles of patients diagnosed with ATBF in Japan, we reported three new ATBF cases at our hospital between May 2015 and April 2018 and conducted a literature review.

Key words: African tick bite fever, rickettsiosis, eschar, spotted fever group rickettsiosis

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Introduction

African tick bite fever (ATBF) is a rickettsiosis caused by *Rickettsia africae*, an obligate intracellular Gram-negative bacterial pathogen transmitted by ticks of the genus *Amblyomma*, mainly *A. variegatum* and *A. hebraeum*. As these vectors are mainly distributed in Sub-Saharan Africa and to a lesser extent in the West Indies (1), ATBF is a common acute febrile illness in Sub-Saharan Africa.

A recent report indicated that spotted fever group rickettsiosis (SFGR) was the cause of febrile illness in 8.7% of hospitalized patients in Tanzania and 22.4% of outpatient pediatric patients in Kenya (2). The most prevalent of all SFGRs in Africa is ATBF (2). Furthermore, ATBF is an important differential diagnosis among travelers with an acute febrile illness who have returned from endemic areas. One study found that among travelers to rural Sub-Equatrial Africa, the incidences of ATBF and SFGR were 4% and 5.3%, respectively. Among such cases, the 5.3% rate of SFGR corresponded to 0.25 cases per person-travel-month (3).

Clusters of cases related to leisure safari tourists, backpackers, hunters, sports competitors, students, foreign aid workers, film crew staff, and soldiers are characteristic of ATBF (1, 3). Among returning travelers, ATBF may be underdiagnosed due to limited diagnostic tests availability and physicians' unfamiliarity with the disease. As there are no national surveillance data on ATBF in Japan, little is known about imported ATBF cases.

This case report and literature review aimed to better characterize the epidemiologic, clinical, and laboratory profiles of patients diagnosed with ATBF in Japan.

Case Reports

Three cases of ATBF were diagnosed between May 2015 and April 2018 at the Disease Control and Prevention Center, National Center for Global Health and Medicine (NCGM), in Tokyo, Japan. A laboratory diagnosis of ATBF was made by the detection of DNA sequences and/or antibody detection at the National Institute of Infectious Diseases. DNA detection was performed by nested polymerase chain reaction (PCR) using primers derived from the rickettsial 17-kDa common protein antigen and the *gltA* gene. A sequencing analysis of the 17-kDa gene was then performed to identify *R. africae*. For antibody detection, serum samples were tested using an indirect immunofluorescent assay for immunoglobulin G (IgG) and immunoglobulin M (IgM) against *R. africae.* Cases were defined according to the diagnostic criteria for ATBF, except for in Case 1 (Table 1) (4).

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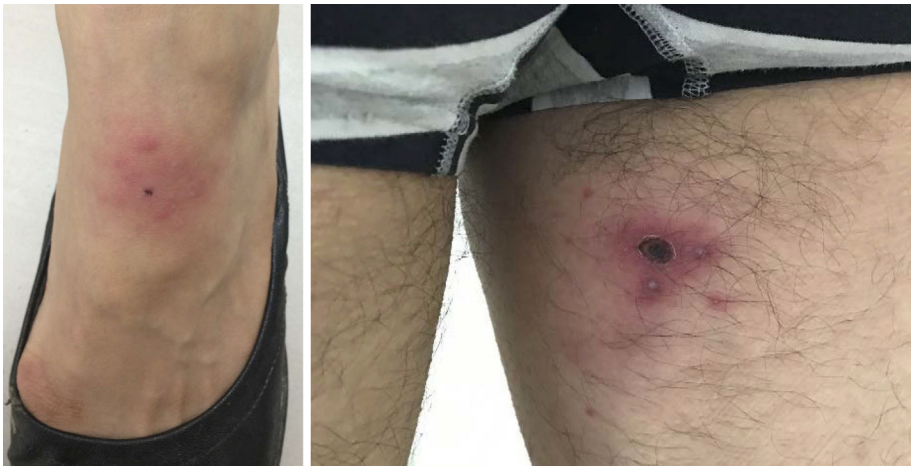
Table 1. Diagnostic Criteria for African Tick Bite Fever[a].

A.	Direct evidence of *Rickettsia africae* infection by culture and/or PCR
	or
B.	Clinical and epidemiological features highly suggestive of ATBF, such as multiple inoculation eschars and/or regional lymphadenitis and/or a vesicular rash and/or similar symptoms among other members of the same group of travelers coming back from an endemic area (Sub-Saharan Africa or French West Indies)
	and
	Positive serology against spotted fever group *Rickettsiae*
	or
C.	Clinical and epidemiological features consistent with a spotted fever group rickettsiosis such as fever and/or any cutaneous rash and/or single inoculation
	and
	Serology specific for a recent *R. africae* infection (seroconversion or presence of IgM ≥1:32), with antibodies to *R. africae* greater than those to *R. conorii* by at least two dilutions, and/or a Western blot or cross-absorption showing antibodies specific for *R. africae.*

[a]A patient is considered to have ATBF when criteria A, B, or C are met.

From Reference (4)

ATBF: African tick bite fever



A B

Figure. (A) An eschar on top of the left foot in Case 1, and (B) an eschar on the inside of the left thigh with surrounding erythematous nodules in Case 2.

Case 1

A 41-year-old woman who had undergone surgery for an acoustic tumor 15 years ago visited South Africa for leisure between May 9 and 15, 2015. She visited Kruger National Park game reserve and Johannesburg and participated in a walking safari and game drives wearing long-sleeved shirts. She used insect repellent and did not recall receiving any tick bites during her visit.

On day 1, she developed a fever, and on day 4, she attended our clinic at the NCGM for a persistent fever. On an examination, she was not acutely distressed; her temperature, blood pressure, and pulse were 36.9 ℃, 110/66 mmHg, and 65 beats per minute, respectively. She had left inguinal lymphadenopathy with tenderness and an eschar with surrounding erythema on the dorsum of the left foot (Figure A), but her physical examination findings were otherwise normal.

Laboratory tests showed slightly elevated levels of C-reactive protein (CRP; 0.89 mg/dL). Two sets of bacterial blood cultures were negative. Acute fever lymphadenopathy and an eschar along with her travel history to an area endemic for ATBF strongly suggested ATBF.

She was treated with doxycycline, 100 mg twice daily for 7 days for ATBF as a cause of the fever. Her condition improved rapidly within a few days of starting treatment. She experienced seroconversion of IgM and IgG against several *Rickettsia* species based on testing 2 serum samples collected 26 days apart. Seroconversion was defined as conversion from negative to positive. At the initial visit, IgG and IgM titers for *R. africae* were both negative; at the second visit, her IgG and IgM titer were 1:160 and 1:320, respectively. The highest titer of IgM was observed against *R. africae*, with the IgM for *R. conorii* being 1:160.

We diagnosed the patient with ATBF based on clinical, epidemiologic, and serologic findings, although the difference in the titer between *R. africae* and *R. conorii* was only one dilution.

Case 2

A previously healthy 45-year-old man visited South Africa to conduct a mosquito survey between December 1 and 17, 2016. He stayed in Ka-Bungeni, a large village near the border between South Africa and Zimbabwe. He used a repellent (DEET; N,N-diethyl-m-toluamide). On day 1, he presented with a fever, myalgia, arthralgia, and lethargy, and on day 7, he attended our clinic at the NCGM. On a physical examination, his temperature, blood pressure, and pulse were 36.7 ℃, 150/98 mmHg, and 62 beats per minute, respectively. The other physical examination findings were normal except for conjunctival congestion, left inguinal lymphadenopathy, and an eschar on the inner right thigh (Figure B). He reported that he had developed multiple eschars during his stay in South Africa that had gradually improved, except for one remaining eschar.

Laboratory tests showed slightly elevated levels of aspartate aminotransferase (47 U/L), alanine aminotransferase (45 U/L), and CRP (1.89 mg/dL). Blood samples were taken for serology, and two sets of bacterial blood cultures were negative. The presence of an acute fever and multiple eschars along with his travel history to an area endemic for ATBF strongly suggested ATBF. He was treated with doxycycline, 100 mg twice daily for 7 days. His condition improved rapidly within a few days of starting treatment. He experienced seroconversion of IgM and IgG against *R. africae* based on testing 2 serum samples collected 12 days apart. At the initial visit, his IgG and IgM titers for *R. africae* were both negative; at the second visit, IgG and IgM titers were both 1:320. The highest titer of IgM was observed against *R. africae*, with the IgM for *R. conorii* being 1:160. We diagnosed the patient with ATBF based on diagnostic criterion B (Table 1).

Case 3

A previously healthy 54-year-old woman visited South Africa for wildlife volunteering between March 11 and 26, 2018. She stayed at Nelspruit and Johannesburg and visited game reserves. She did not recall receiving any tick bites during her visit. On day 1, she developed a fever, left inguinal lymphadenopathy, and an eschar on the inner right thigh. On day 6, she developed a diffuse rash on her trunk, and on day 7, she presented to our clinic at the NCGM.

On an examination, she was acutely distressed and had a temperature of 36.3 °C, a blood pressure of 124/99 mmHg, and a pulse of 71 beats per minute. A physical examination showed inguinal lymphadenopathy; macular edematous erythema on the trunk, face, and lower extremities; and an eschar on the inner right thigh. Laboratory tests showed mildly elevated levels of CRP (3.03 mg/dL). The acute fever, lymphadenopathy, diffuse rash, and presence of an eschar along with a history of contact with wild animals and game reserves in an area endemic for ATBF strongly suggested ATBF.

A skin biopsy was performed for the identification of *R. africae*, and she was treated with doxycycline, 100 mg twice daily for 7 days. Her condition improved rapidly within a few days of starting treatment. Thereafter, a DNA sequence analysis of the gene encoding the rickettsial 17-kDa common protein antigen revealed that it was identical to an *R. africae* gene. In this case, serological testing was not performed. We diagnosed the patient with ATBF based on diagnostic criterion A (Table 1).

Discussion

Our case series described the diagnosis of ATBF in three Japanese travelers who presented to our hospital. A literature search revealed five published reports describing an additional seven Japanese cases of ATBF (5-9). Table 2 presents the clinical information, including symptoms, physical and laboratory findings, and diagnostic test results associated with the three cases diagnosed at the NCGM and the seven previously reported cases (5-9).

Sub-Saharan African countries in which ATBF is endemic include South Africa, Mozambique, Kenya, Tanzania, Zimbabwe, and Botswana (3, 10). Few Japanese travelers have contracted ATBF, judging from current reports. The areas in which these Japanese travelers contracted ATBF include South Africa (70%), Mozambique (20%), and Zimbabwe (10%). We did not find any Japanese travelers who contracted the disease in the West Indies, where ATBF is also endemic. The source countries may reflect the travel destination preferences among Japanese travelers. In our case series, there was also one cluster reported (Cases 7 and 8). A seroepidemiological study showed that 8.6% of first-time travelers to Sub-Saharan Africa acquired ATBF (11). Therefore, it is important not to overlook the possible diagnosis of ATBF.

ATBF usually results from bites by ticks infected with *R. africae*. Jensenius et al. (3) reported that risk factors for ATBF in travelers include game hunting, travel to southern Africa, and travel during November through April. According to this study, game viewing was the most common risk factor, as visitors to game reserves are exposed to ground vegetation and high grass, in addition to cattle and wild ungulates, which are the primary reservoirs of *Amblyomma* spp. Furthermore, a serological survey reported an increased prevalence of antibodies to *R. africae* among indigenous people living in lowland forests who participated in bush activities associated with a high incidence of tick bites (12). Another study showed that the risk factors for SFGR (mostly ATBF) among travelers include older age, being a man, traveling to southern Africa, travel between March and May, and traveling for tourism (10). In two studies on ATBF risk factors, the seasonality for an increased risk of contracting ATBF was slightly different; however, in both studies,

Table 2. **Clinical Characteristics and Findings Associated with African Tick Bite Fever in Japanese Travelers.**

Case[a]	Age (years)	Sex	Area of infection	DOS (days)	Purpose of travel	MOT	Incubation period (days)	Cluster	Symptom	Lymph nodes (site)	Eschar number location	Rash besides eschar	Tick bite history	Diagnostic method	OTD (days)	CR within 72 h
1	41	F	Ka-Bungeni, South Africa	7	Tourism	May	3-9	No	Fever, arthralgia	Inguinal	1 Left ankle	Erythema	No	Serology for *R. africae*	4	Yes
2	45	M	Kruger National Park, South Africa	17	Research	Dec	2-18	No	Fever, arthralgia, lethargy	Inguinal	2 Both thighs	Vesicular	No	Serology for *R. africae*	7	Yes
3	54	F	Kruger National Park, South Africa	16	Volunteer	Mar	4-19	No	Fever	Inguinal	1 Right thigh	Vesicular	No	Eschar PCR for gltA, 17 kDa	7	Yes
4	45	M	Kimberley, South Africa	3	Tourism	Feb	-	No	Fever, headache	Inguinal	1 Left buttock	Erythema	No	Serology for SFGR[b]	-	Yes
5	40	M	Zimbabwe	4	Research	Mar	12	No	Fever, lethargy	Inguinal	1 Left lumber	Erythematous papules	Yes	Serology for *R. conorii*[b]	12	No
6	34	M	South Africa	20	-	Mar	0-9	No	Fever, erythema	-	1 Left lumber	Erythema	No	Serology for *R. conorii*[b]	6	-
7	30	F	Mozambique	-	-	May	10	Yes	Fever, headache	Inguinal	3 Lower extremities and trunk	Papules	Yes	Serology for *R. conorii* +eschar PCR for gltA, 17 kDa, ompA	-	No
8	55	M	Mozambique	-	-	May	5	Yes	Fever, headache, lethargy, myalgia	Inguinal	1 Lower extremities	Papules	Yes	Serology for *R. conorii*	-	No
9	61	F	Kruger National Park, South Africa	11	Tourism	-	-	No	Asymptomatic	Systemic	>10 All extremities and trunk	Papules	Yes	Serology for *R. conorii* +eschar PCR for gltA, 17 kDa	-	-
10	50s	M	Pilanesberg, South Africa	5 or more	Tourism	Apr	7-17	No	Fever, lethargy	Inguinal	1 Right buttock	Erythema	No	Serology for *R. conorii* +eschar PCR for gltA, 17 kDa	7	Yes

[a]Cases 1 to 3 are described in this report. Cases 4 to 10 were reported in the literature; [b]Cases 4 to 6 did not have a definitive diagnosis (meaning not meet the criteria above fully but diagnosed clinically in each case report).

CR: clinical response, DOS: duration of stay, F: female, M: male, MOT: month of travel, OTD: onset to treatment, PMH: past medical history, *R. Rickettsia*, SFGR: spotted fever group rickettsioses

the risk of contracting ATBF was higher during the rainy season than at other times (3, 10).

The 10 ATBF cases that have been reported in Japan, described in this review, included 6 men and 4 women, with a median age of 45 (interquartile range: 40-54) years old, excluding Case 10 (exact age was unknown) (Table 2). Only one patient engaged in game hunting while traveling, while eight patients were likely to have been exposed to tick bites while hiking in the bush. All cases occurred between November and May, which is the rainy season in many en-

demic areas for ATBF. The purpose of travel included tourism (4 cases) and research (2 cases). Most patients had more than one risk factor, which is similar to what has been reported among other international travelers who contracted ATBF (3). Therefore, taking a detailed history of activities engaged in during travel and considering the seasonality of travel are important clues for suspecting ATBF.

The symptoms of patients presenting to the hospital in Japan were non-specific and included a fever, headache, myalgia, and lethargy. Studies report that more than 80% of patients with ATBF exhibit a fever, headache, and myalgia (3). Among the cases identified in Japan, the common physical findings were lymphadenopathy and a rash, including eschars, which are characteristic of ATBF. Regional lymphadenitis and eschars have been reported in 43-100% and 53-100% of cases, respectively (1). Among patients with ATBF, 21-54% develop multiple eschars. *Amblyomma* spp. ticks, the vector, are very aggressive and attack humans in response to stimuli (1, 13). Among Japanese travelers, regional lymphadenopathy was observed in 90% of the cases, and eschars were found in all cases, including 3 cases with multiple eschars. These findings indicate that both lymphadenopathy and eschars are sensitive signs that are useful for making a diagnosis of ATBF. The eschars were most commonly located on the lower extremities, which are associated with outdoor activities, such as hiking in the bush. Therefore, as a precaution, travelers participating in such activities should be advised to use repellents and protective clothing, such as long-sleeved shirts and long pants, before they travel to endemic areas. However, the effectiveness of such preventive measures may be limited, as is shown by Case 1.

In Japan, there is no commercially available diagnostic test for ATBF. In this case series, nine cases were diagnosed using serology-based diagnostics, and four were diagnosed using molecular-based diagnostics, including three patients diagnosed using both methods. Regarding the serology of patients with ATBF, the median seroconversion times of IgM and IgG were 25 and 28 days, respectively (14). These times are significantly longer than the median seroconversion times reported for other SFGR infections of 9 and 6 days for IgM and IgG, respectively. Therefore, based on previous study reports, blood samples should be collected four weeks apart (1, 2). We also need to interpret the serological test results carefully, as cross-reactivity occurs among entities in the spotted fever group Rickettsiae. In previous cases 4 through 6, ATBF was diagnosed based on the patient history in addition to serology.

A DNA sequencing analysis of an eschar sample is considered standard, but PCR using a non-invasive swab sample is another suitable choice for sample collection. The method of directly swabbing the lesion, such as an eschar or vesicle, has also proven useful, as it enables the early detection when serology is still negative (1, 15-17). However, information concerning the utility of non-invasive swab sampling is limited, and further studies are needed. In Japan, these tests are available only in reference laboratories, such as the National Institute of Infectious Diseases.

The prognosis of ATBF is generally good, with doxycycline being the preferred treatment (1). All cases diagnosed in our hospital responded well to doxycycline. However, 3 of 8 Japanese cases (37.5%), including 7 previously reported cases, showed a delayed response. In Case 5, relapse was suspected because the fever and rash recurred 14 days after minocycline therapy. The treatment was repeated, and thereafter, all symptoms improved. In Cases 7 and 8, systemic symptoms lasted 8 days and 5 days, respectively. Detailed information on these three cases was not available. Previous reports have indicated that patients with ATBF over 65 years old tend to have more severe and longer-lasting symptoms, with a slower recovery than younger patients. In addition, older people more frequently have underlying diseases than younger ones, so particular attention should be paid to older people with suspected ATBF (18). However, Cases 5, 7, and 8 were 45, 30, and 55 years old, respectively. Case 5 had a longer delay between the onset of symptoms and initiating treatment than the other cases, which may have affected the clinical course (Table 2). No other factors associated with a delayed response have been reported.

We also need to acknowledge the main limitation of this study. Due to the retrospective nature of the study, several missing values, especially in previous cases, could not be avoided.

In conclusion, ATBF is a rare imported disease in Japan. However, its incidence may be underdiagnosed due to limited access to diagnostic tests and physicians' unfamiliarity with the disease. Nonetheless, ATBF should be suspected in patients with an acute fever, lymphadenitis, and eschars who have visited areas in Sub-Saharan Africa that are endemic for ATBF.

The authors state that they have no Conflict of Interest (COI).

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