African Tick-bite Fever: Four Cases Among Swiss Travelers Returning from South Africa

Yves Jackson, François Chappuis, and Louis Loutan

Background: African tick-bite fever (ATBF) is a recently described disease belonging to the spotted fever group. It is caused by *Rickettsia africae*, and cases are mainly diagnosed in travelers returning from sub-Saharan Africa.

Methods: We report four cases of ATBF among Swiss travelers returning from a 1-month trip in rural South Africa. Diagnosis was made on the basis of clinical, epidemiologic and serologic findings that we describe in detail. Serology was performed using microimmunofluorescence (MIF) assay 2 weeks, 6 weeks and 14 months after the commencement of symptoms.

Results: All patients developed the typical eschar and a rash; two had a local lymphadenopathy and one a lymphangitic reaction. Two patients developed transient neuropsychiatric symptoms such as headache, irritability and depressed mood. All four patients had rises in both IgM and IgG classes of anti-*R. africae* antibodies. After 1 year, only two patients still had measurable circulating antibodies. Cross-reactions with *R. conorii* were noted. Three patients were cured after a short course of doxycycline; one required 15 days of treatment.

Conclusions: ATBF is a benign disease increasingly being diagnosed in travelers. After ruling out malaria, ATBF diagnosis relies upon a detailed travel history and the classical findings of influenza-like symptoms, fever, one or more necrotic eschars, and rash. Serologic tests usually help to confirm the diagnosis. Neuropsychiatric symptoms specifically associated with ATBF are reported here for the first time.

African tick-bite fever (ATBF) is a rickettsial infection of the spotted fever group. It is caused by a recently isolated rickettsia (*Rickettsia africae*). Several recent articles have reported infection among travelers and natives with specific epidemiologic, clinical and serologic features.[1–3] These features differ from the classical Mediterranean spotted fever (MSF) caused by *R. conorii*, which used to be considered as the only tick-transmitted rickettsial disease responsible for the clinical picture of fever, cutaneous inoculation eschar (tache noire) and rash acquired in Europe or in Africa. Kelly et al. isolated *R. africae* in sub-Saharan Africa in 1990, and reported the first proven case of human infection in 1992.[4–6] *R. africae* is transmitted by a hard tick (*Amblyomma hebraeum* and *Amblyomma variegatum*) which is not host-specific. It infests cattle and wild ungulates, and transmission usually occurs in rural areas. Conversely, *R. conorii* is transmitted by a dog tick (*Rhipicephalus* species), mostly in urban settings. Amblyommas exhibit a host attack strategy and feed readily on humans. This explains the outbreaks of infections among groups of people and the frequent presence of several eschars on the same person's skin.[7–9]

In this article we describe four cases of *R. africae* infection among Swiss travelers acquired during a 1-month trip through South Africa, and discuss the main epidemiologic and clinical features of ATBF.

Patients and Methods

Our study included seven Swiss travelers: four adults and three children from two families. We review the clinical and laboratory findings in the infected and non-infected travelers. Clinical checkup and laboratory testing were performed 2 days after return to Switzerland

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(i.e., 12 to 14 days after the first symptoms occurred) during the acute phase of the illness, and 1 month and 14 months later during the convalescent phase. Standard laboratory tests were done at the Geneva University Hospital, and the serology for *R. africae* and *R. conorii* was performed at the Unité des Rickettsies of the University de la Méditerranée (Marseilles, France) in collaboration with Professor D. Raoult. The method used was indirect microimmunofluorescence (MIF). Serologic titers of IgG $\geq$ 128 and/or IgM $\geq$ 64 were considered as evidence of recent infection.

The visit to South Africa took place during the southern hemisphere winter (Fig. 1). The seven travelers started with a 3-day visit to the Kruger Park, where they undertook game drives without direct animal contact. They then visited KwaZuluNatal province, Free State province and finally the Cape region, ending up at Cape Town. They spent most nights camping in the bush, and did a lot of hiking and horseback riding, mostly during the second week of their stay. Horses were described as being heavily infested with hard ticks, but none of the travelers noticed any tick-bites during this period. They reported frequent contacts with cattle. None of the travelers used insect repellents or antimalarial prophylaxis.

All group members were healthy without any significant medical or psychiatric history, except for patient 5, a 49-year-old man who had spent his childhood in South Africa. He reported having had a rickettsial infection when he was 3 years old. No serologic test was ever done to confirm this, and he had recovered without antibiotic treatment.

After 3 weeks in South Africa, four travelers developed symptoms compatible with an acute rickettsial infection. The chronology of symptoms for each of them is given in Figure 2.

Figure 1 Map of South Africa with group itinerary from Johannesburg to Cape Town. The large dot shows where patient 1 had the first symptoms on day 20.

After 3 weeks in South Africa, four travelers developed symptoms compatible with an acute rickettsial infection. The chronology of symptoms for each of them is given in Figure 2.

Patient 1

A 55-year-old man developed fever and diffuse myalgia on day 20 of his visit to South Africa. On day 21, he complained additionally of headaches, neck pain and nausea. He also noticed a single necrotizing eschar with a mild lymphangitis (Fig. 3) on his left ankle. Fever and headaches diminished after 3 days, but nausea and malaise continued. On day 29, the patient developed a diffuse maculopapular rash. He also reported mood change such as irritability, starting on day 34.

Patient 2

An 11-year-old boy complained of headaches, severe asthenia and a single eschar without lymphangitis on his left knee on day 24. Two days later, he noticed a tender left inguinal lymphadenopathy and a maculopapular rash. He presented without fever.

Patient 3

A 45-year-old woman complained of hyperesthesia in both arms from day 25. The next morning, she was feverish with severe headaches. On day 27, she noticed a single eschar without lymphangitis behind her left shoulder. Three days later, a generalized pale maculopapular rash developed (Fig. 4), and she complained of severe asthenia and myalgia and neck muscle pain. On day 32, a firm and tender ipsilateral axillary lymphadenopathy appeared. The patient also developed significant irritability with depressed mood.

Patient 4

A 46-year-old woman developed fever, headaches and arthromyalgia on day 25. On the next day, she noticed a single eschar without lymphangitis behind her right knee, and complained of significant nausea. Four days later, she developed a generalized pale maculopapular rash. On day 32, she noticed a firm and tender right inguinal lymphadenopathy.

The three other members of the group (patients 5, 6 and 7) reported no symptoms, except for one (patient 6), who complained of minor headaches without fever which disappeared within 24 h (during the corresponding incubation period of symptomatic patients). Subsequently, she did not present any other symptom evocative of ATBF.

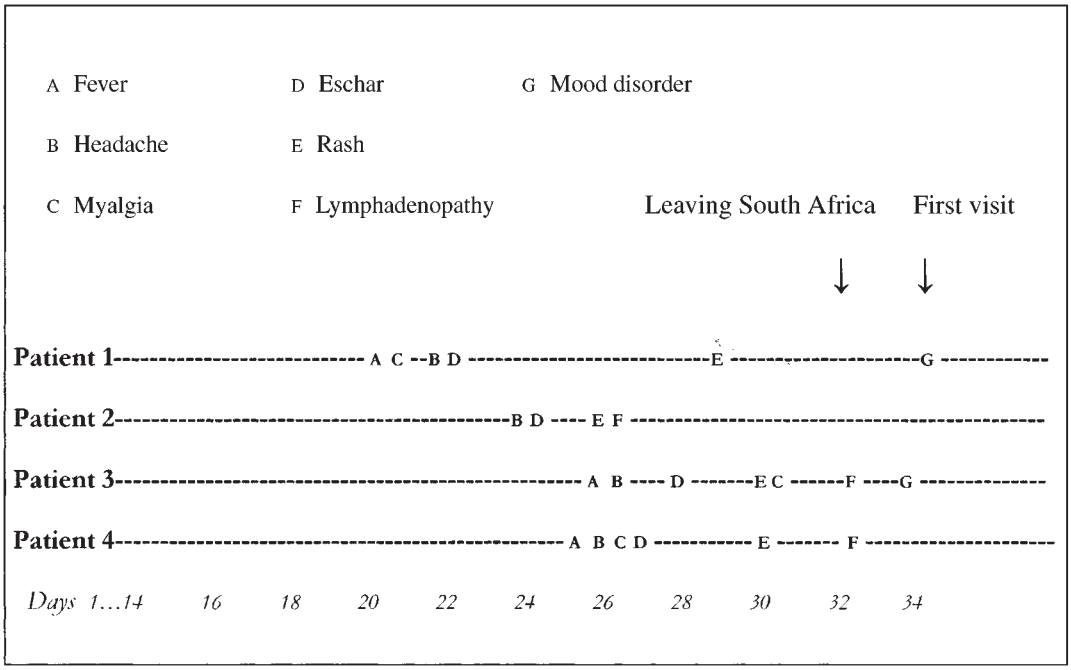

Figure 2 Chronology of symptoms among the four symptomatic patients.

Clinical Testing and Laboratory Results

Table 1 summarizes the major clinical and biological points noted during the first medical visit, 2 days after arrival in Switzerland (i.e., 9 to 14 days after symptoms began).

Note that only patients 1, 3 and 4 developed mild systemic inflammatory reactions with slightly elevated C-reactive protein (CRP) levels. The only significant hematologic finding was very mild leukopenia in patient 3. Patients 2 and 3 showed mild alanine aminotranferase (ALAT) elevations. Patient 2 showed no CRP elevation and, interestingly, he was the only patient with no history of fever.

All the serologic tests were done at the same reference laboratory in Marseille.

Table 2 summarizes the serologic results for *R. africae* and *R. conorii* at the first visit, and 1 month and 14 months later. These results show differences in the kinetics of the serologic responses among the four symptomatic patients. Patient 1, who was the first to become symptomatic, had circulating IgM antibodies 14 days after his first symptoms.

Figure 3 Necrotic eschar with lymphangitis on the ankle of patient 1.

Figure 4 Maculopapular rash on the neck of patient 3.

Table 1 Clinical Signs and Laboratory Tests at the First Medical Visit

Patient	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Age and sex	55 M	11 M	45 F	46 F	49 M	14 F	14 M
Day[a]	14	10	9	9	–	–	–
Fever	–	–	–	–	–	–	–
Eschar	Left ankle	Left knee	Left scapula	Right axilla	–	–	–
Lymphangitis	Mild	–	–	–	–	–	–
Lymphadenopathy	–	Left inguinal	Left axillary	–	–	–	–
Cutaneous rash	Maculopapular, diffuse	Maculopapular, local	Maculopapular, diffuse	Maculopapular, diffuse	–	–	–
Headaches	Present	Present	Present	Present			
Mood disorder	Irritability	–	Irritability, depressive mood	–	–	–	–
Hb (male 140–180 g/L, female 120–160 g/L)	157	130	126	117	145	142	128
Leukocyte (4–11 g/L)	7.3	7.6	3.0	6.9	7.2	8.6	5.9
Platelets (150–350 g/L)	400	345	174	209	276	337	241
C-reactive protein (< 10 mg/L)	17	< 10	25	24	< 10	< 10	< 10
ASAT (male 14–50 U/L, female 8–39 U/L)	29	35	37	32	13	18	19
ALAT (male 13–61 U/L, female 3–42 U/L)	23	61	61	22	12	3	17

[a]Number of days since the commencement of symptoms.

Hb, hemoglobin; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase.

Table 2 Serologic Results for *R. africae* and *R. conorii* at the First Visit (i.e., 10 to 14 Days after First Symptoms), and at the Second, and Third Visits

Patient	*1*	*2*	*3*	*4*	*5*	*6*	*7*
R. africae							
IgG/IgM Day 14	0/16	32/8	0/0	0/0	0/16	0/0	0/0
IgG/Ig M Week 6	64/8	128/16	64/16	128/8	0/16	0/0	0/0
IgG/IgM Month 14	0/0	16/0	16/0	0/0	Not tested	Not tested	Not tested
R. conorii							
IgG/IgM Day 14	0/16	16/8	0/0	0/0	0/16	0/0	0/0
IgG/IgM Week 6	32/8	64/16	64/16	256/8	0/16	0/0	0/0
IgG/IgM Month 14	0/0	16/0	32/0	0/0	Not tested	Not tested	Not tested

Day 14: 14 days after the commencement of symptoms.

Week 6: 6 weeks after the commencement of symptoms.

Month 14: 14 months after the commencement of symptoms.

One month later, this titer was decreasing simultaneously with a rise in IgG titer. Patient 2 also produced a mild humoral response, surprisingly of the IgG type, 10 days after the commencement of symptoms. One month later, both IgM and IgG levels were elevated. Patients 3 and 4 had no circulating antibody 9 days after their first symptoms, but both developed a significant rise within a month. Six weeks after the commencement of symptoms, all patients demonstrated a higher level of antirickettsial IgG but not IgM. One year after infection, two patients (patients 1 and 4) exhibited no circulating anti-*R. africae* antibodies, whereas patients 2 and 3 retained low IgG antibody titers.

Judging by epidemiologic, clinical and biological features, the four symptomatic patients (patients 1, 2, 3 and 4) were considered to be infected by a rickettsia. Judging by serologic testing only, *R. africae* was the certain causative agent for patient 2. Patient 4 had a higher titer for *R. conorii* at the second test, which can be considered a cross-reaction, as clinical and epidemiologic features strongly suggest *R. africae* as the causative agent. Patients 1 and 3 did not have titers sufficient to confirm the diagnosis, but considering the rise in antibody levels and the clinical and epidemiologic aspects of their illness, we concluded that both had suffered an *R. africae* infection. As shown by Fournier et al., early antibiotic treatment can reduce

antibody titers,[10] and this could explain this situation. Patient 5 had only very weak IgM titers for both rickettsiae. As mentioned earlier, there was a suspicion of a rickettsial infection in his early childhood, but the very low titer cannot be considered to be a diagnostic immune scar.

All four infected patients received oral doxycycline 100 mg b.i.d. for 5 days. They reported very quick clinical improvement within 1 or 2 days. A second medical visit 5 days after treatment initiation confirmed that three patients (patients 2, 3 and 4) had enjoyed a very good clinical response with improvement of general status and regression of eschar, rash and lymphadenopathy. Patient 1 continued to complain of malaise and nausea, and his eschar remained surrounded by significant inflammatory reaction. An additional 10 days of treatment with doxycycline was prescribed to achieve complete cure. The two patients (patients 2 and 4) who presented with important but transient mood disorders (irritability and depressed mood) quickly improved with antibiotic treatment. All patients had completely recovered 15 days after treatment initiation. After 14 months, all were asymptomatic.

Discussion

ATBF is a not uncommon disease in rural sub-Saharan Africa, especially in South Africa. Outbreaks have been observed in Lesotho, Zimbabwe, Botswana, Congo and Mozambique.[1,11] Bernit and Raoult also described infections acquired in Guadeloupe (French West Indies), where *Amblyomma hebraeum* is present.[12] A recent Norwegian seroepidemiologic study estimated an impressive 8.6% seropositivity rate among travelers returning from sub-Saharan Africa after short- to medium-length stays.[13] A study conducted in Zimbabwe concluded that there was a strong correlation between the prevalence of *Amblyomma* ticks in the environment and the number of ATBF cases,[14] and that the infection rate increased during the dry season. According to the Norwegian data, it is presumed that a substantial number of travelers seropositive for *R. africae* do not develop a symptomatic infection. Among proven cases, only approximately 45% of people report a tick bite. The incubation time is estimated to be 6 days (±1.5).[1]

Patients usually complain first of a low-grade fever, influenza-like symptoms, sometimes arthralgia and photophobia. Aphtous stomatitis has also been described. Clinical status may reveal one or several necrotic eschars, which are sometimes complicated by local lymphangitis. This is a very evocative sign in a febrile patient returning from sub-Saharan Africa. A regional lymphadenopathy and a discrete cutaneous rash (maculopapular or, more rarely, vesicular or purpuric) is seen in less than 50% of infected patients a few days after the first symptoms. Eschar prevalence seems to differ according to studies. Fournier et al. found it in 13/13 patients in a retrospective study concerning very symptomatic patients consulting at a hospital.[1] Jensenius et al.[2] found it in only 50% of patients screened for ATBF after development of flu-like symptoms in sub-Saharan Africa. This could mean that a mild form of the disease exists without development of an eschar. In our study, only one patient presented with local lymphangitis, and he had no palpable lymphadenopathy. Hepatosplenomegaly is rarely mentioned in the literature. Meningeal irritation signs such as headache, neck stiffness or neck muscle pain might also be noticed by the clinician, and might reflect transient infection of the central nervous system (CNS) . In our study, two patients out of four, without any psychiatric history, suddenly developed significant irritability and depressed mood, 10 and 14 days respectively after commencement of the first symptoms and a few days after having presented with neck muscle pain and headache. In one of them, there was a 7-day interval between the disappearance of head and neck pain and the appearance of irritability. The other patient presented with irritability and depressed mood directly after the appearance of meningeal irritation signs. The neuropsychiatric symptoms completely disappeared after a few days of antibiotic treatment. Unfortunately, we did not perform a complete neurologic and neuropsychological examination before treatment initiation. These specific neuropsychiatric symptoms have not been previously described among ATBF cases, and their exact prevalence in ATBF is currently not known. Other rickettsiae (including *R. conorii and R. rickettsii*) infections are capable of provoking neurologic symptoms, mostly caused by encephalitis and, rarely, meningitis.[15] These are probably secondary to a microvasculitic process. Jensenius et al. recently suggested that nuchal stiffness and neck muscle pain in patients with ATBF reflect transient CNS infection.[16] Articles dating back to the time when ATBF was not differentiated from MSF, and reporting on patients with neurologic involvement, may have included ATBF cases.[15,17] Nevertheless, no case of proven meningitis or meningoencephalitis secondary to *R. africae* has ever been reported.

Frequent laboratory findings may include elevated CRP and lymphopenia, and more rarely mild thrombocytopenia and liver enzyme elevation. As illustrated here, serology can remain negative 10 days after the beginning of symptoms. Thus the decision on early presumptive treatment relies mostly on clinical and epidemiologic findings. Definitive diagnosis can be confirmed later by immunologic tests, using MIF assay of a serum sample. Diagnostic criteria include the presence of serum IgM antibodies during the acute phase or a four-fold rise of the titer of IgG antibodies on a convalescent-phase serum sample (usually 1 month after the beginning of symptoms). Several studies have shown that cross-reactions with other rickettsiae of the spotted fever group are very common.[7,10]

Raoult et al. showed that the combination of an MIF assay, a Western blot and a cross-adsorption assay was the most efficient diagnostic strategy actually available.[7] Nevertheless, this achieved a diagnostic sensitivity of 56% only, when PCR was used as gold standard. Culture from an eschar biopsy specimen is also potentially very effective, using molecular techniques with PCR, and using *ompA*-derived primer to isolate and type the rickettsia. Unfortunately, these techniques are currently only available in highly specialized laboratories.[7]

As with other types of rickettsiosis, patients usually respond very well to a short course of oral doxycycline or ciprofloxacin treatment. The latter is recommended for children under 8 years of age, even if there is no absolute certainty concerning the safety of fluoroquinolone in young children. Most practitioners and pediatricians would still prescribe it when indicated. A recent article showed that early doxycycline therapy may prevent the development of anti-*R. africae* antibodies in a significant number of cases, which may lead to diagnostic uncertainties.[10] Unlike with MSF and Rocky Mountain spotted fever, the evolution seems always benign, and no death has ever been reported among patients infected with *R. africae*. Recently, Jensenius et al. mentioned cases of reactive arthritis after infection with *R. africae*.[16] There is currently no information on long-term immunity after a first infection. In our study, we observed that circulating antibody levels fell markedly after 1 year.

Preventive measures include avoiding tick-infested areas, wearing long clothes impregnated with new synthetic pyrethroids or permethrin, and the topical use of a DEET repellent on exposed skin.[8] Frequent screening of the entire body for ticks allows early removal, but ticks might be very small or invisible on black skin. Ticks removed within 24 h after attachment have a very low probability of transmitting infection.[8] The best way to remove ticks includes the use of blunt, rounded forceps. This should be followed by adequate disinfection and a tetanus booster if needed. Antibiotic prophylaxis after a tick bite is not currently recommended in the literature, in view of the benign nature of the disease.

Conclusions

South Africa, Botswana, Namibia and East Africa are increasingly popular destinations for tourists. ATBF, presenting with fever, headache, rash, eschars and neuropsychological symptoms, may cause serious worry to the returning traveler. ATBF should be high on primary care physicians' differential diagnosis list after ruling out malaria, even if the patient does not report any tick bite. This is even more important because a cheap and very efficient treatment is available.

References

1. Fournier PE, Roux V, Caumes E, et al. Outbreak of *Rickettsia africae* infection in participants of an adventure race in South Africa. Clin Infect Dis 1998; 27:316–323.
2. Jensenius M, Hasle G, Henriksen AZ, et al. African tick-bite fever into Norway: presentation of 8 cases. Scand J Infect Dis 1999; 31:131–133.
3. Brouqui P, Harle JR, Delmont J, et al. African tick-bite fever. An imported spottless rickettsiosis. Arch Intern Med 1997; 157(1):119–124.
4. Kelly PJ, Mason PR. Serological typing of spotted fever group rickettsia isolates from Zimbabwe. J Clin Microbiol 1990; 28:2302–2304.
5. Kelly PJ, Matthewman LA, Beati L, et al. African tick-bite fever—a new spotted fever rickettsiosis on an old name. Lancet 1992; 340:982–983.
6. Kelly PJ, Beati L, Matthewman LA, et al. A new pathogenic spotted fever group rickettsia from Africa. J Trop Med Hyg 1994; 97:129–137.
7. Raoult D, Fournier PE, Fenollar F, et al. Rickettsia africae: a tick-borne pathogen in travelers to sub-Saharan Africa. N Engl J Med 2001; 344(20):1504–1510.
8. Parola P, Raoult D. Ticks and tick-borne bacterial diseases in humans: an emerging infectious threat. Clin Infect Dis 2001; 32:897–929.
9. Jensenius M, Fournier PE, Kelly P, et al. African tick bite fever. Lancet Infect Dis 2003; 3:557–564.
10. Fournier PE, Jensenius M, Laferl H, et al. Kinetics of antibody response in *Rickettsia africae* and *Rickettsia conorii* infections. Clin Diagn Lab Immunol 2002; 9:324–328.
11. Smoak BL, MacClain JB, Brundage JF, et al. An outbreak of spotted fever rickettsiosis in US Army troops deployed to Botswana. Emerg Infect Dis 1996; 2:217–221.
12. Bernit E, Raoult D. African Rickettsia infection. Presses Med 1999; 28(26):1428–1432.
13. Jensenius M, Hoel T, Raoult D. Seroepidemiology of *Rickettsia africae* infection in Norwegian travellers to rural Africa. Scand J Infect Dis 2002; 34:93–96.
14. Kelly PJ, Mason PR, Matthewman LA, et al. Seroepidemiology of spotted fever group rickettsial infections in humans in Zimbabwe. J Trop Med Hyg 1991; 94:304–309.
15. Raoult D, Weiller PJ, Chagnon A, et al. Mediterranean spotted fever: clinical, laboratory and epidemiological features of 199 cases. Am J Trop Med Hyg 1986; 35(4):845–850.
16. Jensenius M, Fournier PE, Vene S, et al. African tick-bite fever in travelers to rural sub-equatorial Africa. Clin Infect Dis 2003; 36:1411–1417.
17. Raeber PA, Winteler S, Paget J. Fever in the returned traveller: remember rickettsial diseases. Lancet 1994; 344:331.