IMPORTED SPOTTED FEVER RICKETTSIOSES IN UNITED STATES TRAVELERS RETURNING FROM AFRICA: A SUMMARY OF CASES CONFIRMED BY LABORATORY TESTING AT THE CENTERS FOR DISEASE CONTROL AND PREVENTION, 1999–2002

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Abstract. The increasing popularity of foreign travel and ecotourism places travelers at increased risk for certain tick-borne diseases. From 1999 through 2002, 31 cases of imported spotted fever-group rickettsioses (SFGR) in United States residents reporting travel to Africa were confirmed by laboratory testing at the Centers for Disease Control and Prevention. Nineteen patients (61%) reported visiting South Africa prior to illness onset. Most patients reported fever and one or more eschars; rash was reported for only 26% of the patients. Twelve patients had an initial non-reactive acute-phase serum sample obtained a median of three days after illness onset, and were confirmed by testing a second convalescent-phase serum sample obtained a median of 32 days after illness onset. Five patients were confirmed positive through immunohistochemical staining of skin biopsies, including three patients with acute-phase serum samples that tested negative for SFGR. This study emphasizes the importance of evaluating convalescent-phase serum specimens 28 days or more after illness onset or examining skin biopsies by immunohistochemical staining during early infection to confirm a diagnosis of imported SFGR.

INTRODUCTION

Travel to some foreign destinations may place United States travelers at increased risk for tick bites and infection with tick-borne pathogens, such as spotted fever-group rickettsiae (SFGR). The SFGR most commonly associated with infection in travelers returning from Africa is *Rickettsia africae*, which causes African tick bite fever (also called tick typhus) and is transmitted by ticks of the genus *Amblyomma* in sub-Saharan Africa and in some islands of the French West Indies. Although African tick bite fever is not a nationally notifiable disease in the United States, clinical and epidemiologic information for patients is often provided to the Centers for Disease Control and Prevention (CDC) when specimens are submitted for diagnostic testing. The last review of imported SFGR in the United States was published in 1988 and included 52 cases of imported SFGR in travelers returning from Africa confirmed by laboratory testing at CDC from 1977 through 1986. This report provides a contemporary review of imported SFGR in United States travelers returning from Africa from 1999 through 2002.

MATERIALS AND METHODS

Clinical and epidemiologic information were reviewed for patients with a travel history to Africa and for whom laboratory testing at CDC indicated evidence of infection with SFGR. In addition, epidemiologic information was reviewed for patients with a compatible clinical and travel history, but for whom laboratory testing was negative for SFGR. Because a serologic assay specific for *R. africae* was not available at CDC and extensive antibody cross-reactivity exists among the SFGR, cases were diagnosed serologically by using an indirect immunofluorescence antibody assay to detect IgG antibodies reactive with *R. conorii* and *R. rickettsii*, and in some cases *R. akari* antigens. These assays detect antibodies reactive with various SFGR, including *R. africae*, but cannot definitively ascribe the species responsible for infection. When eschar or rash biopsy specimens were available, infection was diagnosed by immunohistochemical (IHC) staining of SFGR in tissues. In a similar manner, this assay is SFGR-specific but cannot be used to definitively speciate the causative agent. A confirmed case was defined as illness in a patient with at least a four-fold change in SFGR antibody titer between paired serum specimens or SFGR-positive IHC staining in a skin biopsy specimen. A probable case was defined as illness in a patient with a single SFGR antibody titer ≥ 64.

RESULTS

During 1999 through 2002, 31 cases of disease caused by SFGR were identified in United States travelers returning from Africa by laboratory testing at CDC (Table 1); 18 were confirmed cases and 13 were probable cases. Of patients with confirmed infections, 13 (72%) showed a four-fold or greater change in antibody titer, 3 (17%) showed a four-fold change in antibody titer and IHC staining of SFGR in a skin biopsy specimen, one was confirmed by IHC staining and a single supportive antibody titer to SFGR, and one was confirmed by IHC staining as the sole diagnostic test. Among the 16 patients with confirmed infections who had paired sera available for testing, 12 showed seroconversion with a first serum titer ≤ 32 and a second serum geometric mean titer (GMT) of 575 (range = 128–4,096), 2 had a four-fold or greater increase with a first serum GMT of 91 (range = 64–128) and a second serum GMT of 1,024 (range = 512–2,048), and 2 had a four-fold or greater decrease in titer with a first serum GMT of 11,585 (range = 8,192–16,384) and a second serum GMT of 362 (range = 64–2,048). Among the 13 cases with single supportive titers, the GMT to SFGR was 799 (range = 64–32,768).

Of the 30 patients that had serum specimens available for testing, 12 (40%) had an initial acute-phase antibody titer reactive with SFGR ≤32, and were only diagnosed by sero-
logic testing of a convalescent-phase serum specimen. A specific date of illness onset was provided for 10 of these patients whose initial tests results were negative; the median time from illness onset to first serum collection was three days (mean = 3.6 days, range = 0–17). The median time from illness onset to submission of a confirmatory convalescent-phase serum sample for these patients was 32 days (mean = 37.1, range = 25–64). During this same time period, at least 19 patients with suspected African tick bite fever (based on travel history to Africa) had non-reactive serum specimens obtained less than 28 days after illness onset (median = 6 days, range = 1–21). None of these patients had a convalescent-phase specimen obtained ≥ 28 days after illness onset submitted for testing, and their illnesses could not be confirmed as African tick bite fever.

Because clinical and demographic data were collected passively, the information available for each patient varied. Of the 31 patients described in this report, 22 (71%) were male, and the median age was 48 years (range = 11–68 years). Month of illness onset was provided for 25 patients, of whom 12 (48%) reported onset during March or April (Figure 1). A history of tick or other insect exposure was noted for 24 (77%) patients. Fever was reported for 23 (74%) patients and eschar was reported in 17 (55%), including five patients who reported multiple eschars. Eight patients (26%) reported a rash, most frequently maculopapular. Other frequently reported symptoms included headache, myalgias, chills, and lymphadenopathy.

All patients reported recent travel to Africa. Single country designations were available for 22 patients, including South Africa (19), Zimbabwe (2), Rwanda (1). In addition, one patient reported travel to both South Africa and Mozambique, and one traveler reported visiting both Zambia and Tanzania. Seven patients reported travel to Africa, but specific country information was not provided.

![Figure 1](image.png)

**FIGURE 1.** Month of illness onset for imported spotted fever group rickettsial infections in United States travelers returning from Africa.
DISCUSSION

During 2000, approximately 27 million United States travelers visited overseas destinations and approximately 2% reported visiting Africa.10 Many overseas travelers reported participating in outdoor activities while abroad that could result in contact with ticks; for example, 9% of travelers visited national parks, 5% camped or hiked, 5% visited sites of environmental or ecologic interest, and 3% hunted or fished at their foreign destinations.10

Of the 31 patients described in this review, most reported travel to southern or eastern Africa, and 61% reported travel only to South Africa. This observation is similar to other published findings, which suggests that a high proportion of imported SFGR cases diagnosed in travelers are acquired in southern Africa. A review of tick typhus cases diagnosed by CDC from 1977 through 1986 reported that 67% of patients reported travel to southern Africa.7 A review of imported tick typhus in German travelers from 1992 through 1998 showed that 73% of patients had reported travel in southern Africa, and safari or bush walking was reported as a primary risk factor.11 A prospective study examining incidence of SFGR infections among Norwegian travelers to rural sub-Saharan Africa found an overall incidence of 5.5%; in this cohort, travelers diagnosed with SFGR infections were significantly more likely to have traveled to southern Africa than patients not diagnosed with tick typhus.12 In the Norwegian study, travelers reporting hunting activities were 10 times more likely to be diagnosed with SFGR infection than other travelers.12

Although the laboratory tests that were used to identify the cases described in this report do not permit the designation of a specific SFGR species as responsible for infection, the SFGR most commonly described in patients traveling to southern or eastern Africa is R. africae.1 In addition, the predominant clinical pattern observed in these patients (i.e., presence of one or more eschars and relatively infrequent reports of rash) are most consistent with descriptions of disease caused by R. africae.12–15 However, several other SFGR, including R. conorii, R. aeschlimannii, or R. akari, are known to cause disease in sub-Saharan Africa, suggesting that one or more of these pathogens may have also been responsible for disease in this cohort.5,16,17

In this review, 40% of the patients with imported SFGR infections had an initial acute-phase serum specimen with SFGR antibody titers ≥32; these infections could not have been confirmed without testing a convalescent-phase serum specimen. In addition, during 1999 through 2002, 19 patients with a suggestive clinical picture and travel history could not be confirmed or ruled out as having SFGR infection because convalescent serum specimens were not obtained. Seroconversion during R. africae infection may take several weeks; the reported median time to IgG seroconversion after R. africae infection is 28 days, and less than 15% of patients seroconvert within three weeks of illness onset.18 When physicians use serologic assays to make a diagnosis, both acute- and convalescent-phase serum samples should always be tested to confirm a diagnosis. For patients with suspected African tick bite fever, convalescent-phase samples should be collected at least four weeks after illness onset.18 Physicians should also consider submitting cutaneous biopsy specimens from eschars for IHC staining in patients for whom serum specimens are not available, or to confirm a diagnosis early during infection before seroconversion is expected; in this review, three of five patients confirmed by IHC staining of skin biopsies had concurrent acute-phase serum samples submitted that tested negative for antibodies to SFGR, demonstrating the value of IHC during early infection. Physicians should initiate treatment on the basis of compatible clinical findings (e.g., fever and eschar) and epidemiologic features (e.g., travel history to an enzootic country) prior to receiving the results of laboratory tests.

Because R. africae causes illness 1–2 weeks following a bite from an infected tick, the onset of clinical signs in some travelers may occur after their return to the United States. Physicians should therefore consider this diagnosis for febrile patients with a compatible foreign travel history, especially in travelers reporting illness onset in late spring and early summer. In this study, 48% of the cases reported illness onset in March or April, corresponding with the late rainy season in southern Africa. Possible explanations for this finding include times of peak tick activity in enzootic regions, or peak months for tourism and travel. A similar temporal clustering of illness onset in April has been previously reported among European travelers.12 Although specific group travel information was not available for these cases, similarities in dates of illness onset, travel designations, and surnames suggest several group exposures in this cohort. Outbreaks of African tick bite fever have been described among travel groups returning from Africa,6,14 and physicians suspecting SFGR infection in a traveler returning from Africa or other enzootic areas such as the French West Indies should consider the possibility of infection in other members of the patient’s travel group.

Patients may be at risk for different SFGR infections when visiting other parts of the world. During this study period, a patient returning from travel to Australia and Indonesia was serologically confirmed with SFGR infection at CDC; in this patient, infection was most likely due to R. australis, the etiologic agent of Queensland tick typhus.19 In addition, a probable case of SFGR was diagnosed in a traveler to India; in this case, infection with R. conorii (the agent of Mediterranean spotted fever) is most likely.15 Rickettsia conorii has been previously described in southern Europe, Africa, and the Middle East, and travelers to these regions should be aware of the possibility of infection following exposures to ticks or tick-infested environments.15,20

Persons traveling to foreign destinations where tick bites are possible should protect themselves against exposure to ticks by performing regular body checks and removing ticks before they attach, wearing long pants and long sleeves, and tucking pant legs into socks or boots when walking or working in tick-infested areas. Use of DEET (N,N-dimethyl-m-toluamide) applied to exposed skin and clothing, or permethrin-treated clothing, may also help repel ticks. If signs of illness develop within two weeks of a tick bite, patients should consult a physician and report their travel history and tick exposure.

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