Murine Typhus in Returned Travelers: A Report of Thirty-Two Cases

Gaëlle Walter, Elisabeth Botelho-Nevers, Cristina Socolovschi, Didier Raoult, and Philippe Parola*

Unité de Recherche en Maladies Infectieuses et Tropicales Emergentes (URMITE), UMR CNRS-IRD,
WHO Collaborative Center for Rickettsial Diseases and Other Arthropod-borne Bacterial Diseases, Marseille, France;
Service Maladies Infectieuses et Tropicales, Hôpital Nord, Marseille, France

Abstract. Murine typhus, caused by *Rickettsia typhi* and transmitted mainly by the rat fleas, *Xenopsylla cheopis*, has emerged in the field of travel medicine. We analyzed retrospectively the epidemiological, clinical, and biological characteristics of the 32 murine typhus cases that were diagnosed during the past 3 years at the World Health Organization Collaborative Center for Rickettsial diseases, Marseille, France. All of the cases occurred in travelers and most of them had returned from Africa ($N = 13$ of 32) and South-east Asia ($N = 12$ of 32). Exposure to rats was reported only in a few ($N = 2$ of 32) patients. Almost half of the cases were diagnosed in August and September. Only four patients presented the classic triad: fever, rash, and headache. Moreover, we report the first known cases of a hemophagocytic syndrome associated with this disease. Murine typhus must be considered as an etiologic agent of febrile illness in returning travelers, particularly in those with unspecific symptoms.

INTRODUCTION

Murine typhus is acute zoonotic infection caused by *Rickettsia typhi*, an obligate-intracellular, gram-negative bacterium belonging to the typhus group within the order Rickettsiales.¹ Murine typhus is a flea-borne rickettsiosis. The rat flea, *Xenopsylla cheopis* has been considered as the main vector²; the major sources of human infection are flea bites and the contamination of the respiratory tract or excoriated skin with infected flea feces.³

Murine typhus has a worldwide distribution, with the majority of cases occurring in the coastal tropical and subtropical regions⁴; although murine typhus has been recently shown to be a significant cause of fever of unknown origin in the tropics,⁵ cases are rarely documented. The disease has, however, been documented as an emerging or reemerging diseases in several areas such as Hawaii, which had six cases per year before 2002 and 47 cases reported during 2002.⁶ In Tunisia, Letaïef and others⁷ published the first report of seven native cases of murine typhus in 2004, underlining an emergence of this probably underdiagnosed or misdiagnosed disease in that country. In Japan the first serologically diagnosed case of murine typhus was reported in 2004, showing the reemergence of this disease. Indeed, in the 1940s and 1950s many murine typhus cases were reported in Japan, but since 1958 no serologically confirmed cases have been reported.⁸

The increase in international traffic for various reasons, such as tourism, professional interests, and family matters, results in greater vulnerability of travelers throughout the world to the transmission of old, new, and reemerging infectious diseases. During their trip, travelers are exposed to unusual infectious diseases, and the main symptom that is frequently present in ill returnees is fever.

Rickettsial diseases are increasingly being diagnosed in international travelers⁹; a recent study of $\approx 7,000$ returnees who had fever as their chief reason to seek medical care suggests that 2% of imported fevers are caused by rickettsioses and that 20% of these patients are hospitalized.¹⁰

Murine typhus has been reported in ~ 60 travelers since 1983, when the first case of murine typhus in travelers was described.^{4,9,11} Recently, the Geosentinel Network investigated the epidemiology of rickettsial diseases among 99,355 ill returned travelers between 1996 and 2008. A total of 280 rickettsial diseases were analyzed¹²; the majority of the reported rickettsial diseases were spotted fever rickettsioses, however 10 cases of murine typhus were also documented. Southeast Asia was the most common region of exposure that was reported for murine typhus and no complications were noted for any of the cases.¹²

In this work, we report the results of a retrospective analysis of the cases of murine typhus that were diagnosed in our World Health Organization (WHO) Collaborative Center for Rickettsial diseases and other arthropod-borne bacterial diseases between 2008 and 2010.

MATERIALS AND METHODS

We conducted a retrospective study of the murine typhus cases that were diagnosed in our laboratory in Marseille from January 2008 to December 2010. The patients, whose blood samples had been received in our center to be tested for rickettsioses, were included if a microimmunofluorescence assay using the *R. typhi* antigen tested positive under either of the following conditions: 1) a single serum showing immunoglobulin M (IgM) antibody titers $\geq 1/64$ and/or IgG antibody titers $\geq 1/128$ or 2) a 4-fold or greater increase in antibody titers between the acute-phase serum sample and the convalescent-phase serum sample.¹³ When cross-reactions were observed between *R. typhi* and *Rickettsia prowazekii* (the agent of epidemic typhus) and/or between *R. typhi* and the spotted fever group *Rickettsia* spp., including *Rickettsia felis*, another flea-borne rickettsiae, Western blot and cross-adsorption tests were used to discriminate between the species.¹³ A specific quantitative polymerase chain reaction (qPCR) that targeted a fragment of *Rpr 274P* gene coding for hypothetical protein was performed on a DNA sample that was extracted from 200 μ L of an acute-phase serum sample. The sequences of the primers used for the qPCR assay were as follows: Rpr_274.F: 5'-TGT-CAG-ATT-ATA-AAG-ACG-ATG-CTC-AGA-3', Rpr_274.R: 5'-GCA-GCT-TGT-ACT-CCT-TTA-ATT-TGT-TC-3' with the probe: Rpr_274.P: 6-FAM-CCG-CTA-CCG-CAA-ATC-CAT-CAG-A-TAMRA.

*Address correspondence to Philippe Parola, URMITE CNRS-IRD UMR 6236 – Aix-Marseille Université, 27, Boulevard Jean Moulin 13385 Marseille Cedex 05, France. E-mail: philippe.parola@univ-amu.fr

FIGURE 1. Seasonality of murine typhus in French travelers.

The positive control was *R. typhi* DNA, and the negative control was the DNA that was extracted from degenerative cardiac valve.

Clinicians were contacted to obtain clinical and epidemiological data about these patients; this information included age; sex; place of exposure; contact with animals; presence of tick, flea, or lice bites, and past medical history; symptoms (notably fever, rash, and neurological symptoms); and the presence of an eschar and/or lymphadenopathy and treatment.

RESULTS

During the 3-year study period, 32 confirmed cases of murine typhus were discovered. All of the patients were returned travelers. During the same period, our laboratory received 42,276 sera from France and other countries; these samples were been collected from patients who were suspected to have rickettsial diseases. The percentage of *R. typhi* infections in all of the collected sera was 0.06%

($N = 8$ of 14,101) in 2008, 0.07% ($N = 10$ of 14,163) in 2009, and 0.1% ($N = 14$ of 14,012) in 2010. The mean age of the patients with murine typhus was 42 ± 14.5 years (range 1–69). One case of murine typhus occurred in a 1-year-old child. In our study, 50% of the patients were men. Only two patients (6.25%) mentioned an exposure to rats. The majority of the cases of murine typhus (47%; $N = 15$ of 32) occurred in the late summer and early autumn; among them, 25% occurred in August ($N = 8$ of 32), and 22% occurred in September ($N = 7$ of 32). Four cases (12.5%) occurred in February and November. The repartition of cases by month is reported in Figure 1.

Murine typhus was acquired in Africa (Tunisia, Morocco, Ivory Coast, Central African Republic, Madagascar, or Chad) in 40.6% of cases ($N = 13$ of 32) and in Southeast Asia (Indonesia, Philippines, Thailand, Cambodia, Vietnam, Myanmar, or Laos) in 37.5% of the cases ($N = 12$ of 32) (Figure 2). The reason for travel was known for half of the patients and included tourism (6 of 32), business (3 of 32), visiting friends and relatives (7 of 32). Of these destinations, Tunisia and Indonesia were the two most common regions of exposure with 25% ($N = 8$ of 32) and 15% ($N = 5$ of 32) of the cases observed, respectively. Three cases of murine typhus in travelers returning from India/Nepal have been recorded. Two (6.25%) patients were infected in Madagascar and Reunion. One patient was infected in the Canaries islands, and one patient was infected in the Greek islands.

A skin rash was present in 15 cases (47%), headache in 11 cases (34%), and fever in 31 cases ($N = 31$ of 32; 100%). The classic triad of fever, headache, and skin rash was observed in four cases (12%). Two patients presented with life-threatening conditions: one patient presented with septic shock on admission and another patient presented with myocarditis. Other major signs are reported in Table 1; there were no differences in the symptoms of murine typhus

FIGURE 2. Geographical distribution of murine typhus cases in our study. Tunisia with 8 cases are in dark gray; Indonesia and Nepal with 3–5 cases are in middle gray; other countries with 1–2 cases are in light gray.

TABLE 1
Clinical characteristics of 32 patients with murine typhus

Signs	Number (×/32)	%
Fever	32	100
Rash	15	47
Headache	11	34
The classic triad*	4	12
Digestive signs	12	37.5
Hepatomegaly/splenomegaly	5	16
Myalgia/arthralgia	9	28
Confusion	3	9
Septic shock	1	3
Myocarditis	1	3

*The classic triad: fever, rash, and headache.

in patients from Africa compared with patients from Asia. An association with malaria caused by *Plasmodium falciparum* was observed in one case and dengue fever was observed in another case. Elevated transaminases were found in 18 cases (56%) and represented the most common biological abnormality. Hematologic abnormalities, including thrombocytopenia, anemia, and leukopenia were reported in 12 cases (37.5%), and renal failure occurred in 3 cases (9%). The hemophagocytic syndrome occurred in 3 cases (9%). Diagnosis using microimmunofluorescence test was positive in 91% of cases ($N = 29$ of 32) in the acute serum and in 93% of cases ($N = 14$ of 15) in the convalescent serum. A Western blot was performed and revealed positive results in all cases. Specific PCR was performed in all acute sera and revealed positive results for only one patient.

Data regarding the antibiotic regimens used were available for 28 cases (87.5%). Among these patients, 14 (50%) received doxycycline alone; 4 (14.3%) received a combination of two antibiotics, including doxycycline plus ceftriaxone ($N = 3$) or plus amoxicillin ($N = 1$); and the others patients ($N = 8$ of 28, 28.6%) received various other antibiotics including fluoroquinolone, third-generation cephalosporin, penicillin, macrolide, and rifampicin. In two cases (7.2%) no antibiotic was given. All of the patients recovered.

DISCUSSION

In this work, we report the largest series of murine-typhus infections in travelers, including three cases (acquired in Tunisia) that had been recently reported¹³; all of the cases met the diagnosis criteria of murine typhus using reference methods. The emergence of murine typhus and others rickettsioses may encourage physicians to consider a diagnosis of rickettsial disease when confronted by fever in returned travelers. The exposure of travelers to murine typhus is now a reality caused by the emergence of this disease in tropical and subtropical countries and because of an increase in the collective number of trips that have been made throughout the world in recent years. Contact with rodents is seldom noted in the patients' medical histories^{11,13,14}; in this study, contact with rats was documented in only a few cases (< 10%). However, the animal reservoir and the flea vector species that carry *R. typhi* can be broad and diverse depending on geographical location.² In the Korean peninsula the striped field mouse (*Apodemus agrarius*) was the most prevalent (88.9%) rodent compared with the Norway rat (*Rattus norvegicus*) with 0.3%.¹⁵ The flea

species in which *R. typhi* were detected were *Ctenophthalmus congeneroides* and *Rhadinopsylla insolita*. Furthermore, murine typhus has yet another quite different epidemiology with cats and opossums implicated as mammalian hosts with cat fleas as the suggested vector in the United States.²

Travelers to port cities and beach resorts have been reported to be particularly at risk of acquiring *R. typhi* infections.¹² Murine typhus has been mainly described in travelers returning from Indonesia.^{4,11,12} In this country, recent investigations of 137 patients with fever have led to the diagnosis of murine typhus in 6.5% of cases.¹⁶ Tunisia is also known to pose a risk for autochthonous murine typhus, although the disease is underdiagnosed or frequently misdiagnosed.⁷ Others destinations have also been associated with murine typhus in travelers, including Mediterranean countries such as Crete, Spain, Italy, Cyprus, and Egypt.¹³ For travelers in Southeast Asia, the countries of Thailand, Vietnam, Myanmar, Laos, India, and Nepal are also known to pose a risk. Previously, murine typhus has been reported in travelers returning from Vietnam and India.^{17,18} Seroprevalence surveys conducted in this region have shown the presence of murine typhus in Nepal, Thailand, Cambodia, Myanmar, and Laos. In contrast to Southeast Asia, very few data are available for cases of murine typhus in sub-Saharan Africa. Only one serosurvey was conducted in the Central African Republic, where 1.4% ($N = 2$ of 144) of the sera tested were positive for *R. typhi*.¹⁹ In our series, three cases of murine typhus were acquired in this area (Central African Republic, Chad, and Ivory Coast).

Cases of murine typhus have been previously reported during the summer and autumn, which are the main periods of travel for European people. In our series, almost half of the cases were diagnosed in August and September. The seasonal incidence seems to correlate with the abundance of fleas during the late summer and early fall in endemic areas.²⁰

Fever is common in ill returnees, but it is a nonspecific sign. Fever not only could be a sign of a community or tropical infectious diseases but also could be a fever of unknown origin. Fever is the consistent clinical sign in murine typhus. In the Geosentinel study, malaria was identified in 21% of ill returnees with fever, including *P. falciparum* in 14% of the cases¹⁰; other reported diagnoses were dengue fever, salmonellosis, and rickettsial diseases in 2% in this population. However, in 22% of the travelers, the fever was classified as an unspecified febrile illness.¹⁰ Murine typhus has been described as a major cause of acute undifferentiated fever in Indonesia¹⁶ and as a cause of fever of unknown origin. A 2-year prospective study conducted in Vientiane, Laos, identified acute rickettsial infections as the cause of fever in 27% of adults who were both blood-culture and malaria-smear negative. The acute rickettsial infections included *R. typhi* in 9.6% of the cases.⁵ Therefore, murine typhus should be considered by physicians in the differential diagnosis of fever in returned travelers.

Murine typhus can be misdiagnosed in travelers because of their nonspecific symptoms²¹; generally, after an incubation period of 7–14 days, the onset of illness is relatively abrupt and manifests as fever, headache, myalgia, arthralgia and nonspecific gastrointestinal symptoms. Digestive symptoms seem to be particularly frequent in children, occurring in 77% of the children in a study conducted in Texas.²² The rash often appears a week after the onset of fever and is discrete, however, the rash is not always found.² The presence of a rash is

highly variable from one patient to another, ranging from 20% to 80% of cases, depending on the study.¹³ Therefore, the diagnosis of murine typhus should not be considered only for a patient who has a fever and rash. Approximately 50% of the patients who were included in our series presented with mainly a maculopapular rash but also a simple macular rash; one patient had a petechial rash, which remains a relatively rare form. Other common symptoms are cough, hepatomegaly, splenomegaly, and confusion.² The classic triad consists of fever, headache, and rash and was found in 18% of the adult patients who presented in the series in Texas, whereas the triad was found in 49% of the patients in a pediatric series in Texas.^{22,23} Our results were similar to the findings of Dumler and others²³; this triad cannot be considered to be a pathognomonic sign because it is inconsistent. The hemophagocytic syndrome occurred in three cases, but all the diagnostic criteria could be obtained in only one case. To date, hemophagocytic syndrome has been associated with rickettsial diseases, but never with *R. typhi*. This syndrome has been described with *Rickettsia conorii*, *Orientia tsutsugamushi*, and *Ehrlichia chaffeensis*.²⁴

Murine typhus is usually a mild disease; however, severe forms have been reported. In a large study of murine typhus, 2% of the patients had life-threatening cases that resulted in three deaths, including two patients with multi-organ failure.²³ One fatal case involved a woman who, during a trip to Spain, presented with multi-organ failure and hemorrhagic syndrome.²⁵ In our series, despite a case of septic shock and a case of myocarditis, no deaths were observed. Mortality in the absence of antibiotic therapy has been reported up to 4% of cases.²³ Murine typhus could be confused with various infectious diseases, including malaria. Therefore specific antibiotic treatment is necessary.

Doxycycline remains the treatment of choice for murine typhus. Quinolone treatment has been proposed as an alternative.^{26,27} However, treatment with fluoroquinolone has yielded unfavorable outcomes in two cases of murine typhus.^{28,29} Moreover, fluoroquinolone treatment has recently been identified as a risk factor for developing a severe form of Mediterranean spotted fever.³⁰

Rickettsia typhi is one the four rickettsioses that are frequently found in travelers; the three other organisms are *R. conorii*, *Rickettsia africae*, and *O. tsutsugamushi*.⁹ Murine typhus has emerged in the field of travel medicine and may be misdiagnosed because the patients frequently present with nonspecific symptoms. Despite the rarity of complications, this disease is potentially fatal. We herein report the first known cases of a hemophagocytic syndrome that was associated with murine typhus. This disease should be highly suspected in febrile patients returning from the Mediterranean basin, Asia, and Africa. Malaria excluded, rickettsial diseases should be considered in all patients who present with a fever of unknown origin.

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Authors' addresses: Gaëlle Walter, Elisabeth Botelho-Nevers, Cristina Socolovschi, and Didier Raoult, Aix Marseille Université - URMITE UMR, Marseille, France, E-mails: gaellewalter@hotmail.fr, elizabeth.botelho@ap-hm.fr, cristina.socolovschi@univ-amu.fr. and didier.raoult@gmail.com. Philippe Parola, Service des Maladies Infectieuses et Tropicales, Hôpital Nord, Marseille, France, E-mail: philippe.parola@univ-amu.fr.

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