



Case Report

Spotted fever from *Rickettsia typhi* in an older woman: a case report from a geographic area where it would not be expected

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SUMMARY

We describe the case of a 75-year-old woman presenting with spotted fever followed by acute renal failure and septic shock. The infection was caused by *Rickettsia typhi*, not reported in Calabria district (southern Italy) since World War II. The diagnosis of murine typhus was made 3 days after admission and was based solely on clinical criteria when her worsening condition required a prompt move to the intensive care unit. Therapy with tigecycline was then started immediately and the patient improved dramatically. The diagnosis of murine typhus was confirmed 10 days after admission by immunofluorescence assay. Our case is an example of how the diagnosis of murine typhus is challenging. However, in the case of a disease lacking specific symptoms, clinicians should never forget that, even in geographic areas considered free of flea-borne diseases, the components of the enzootic cycle are present and the diagnosis should never be underestimated.

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1. Introduction

Murine typhus (MT) is a flea-borne infection caused by *Rickettsia typhi* (formerly *Rickettsia mooseri*). It has a wide distribution and is endemic to warm coastal areas. Transmission to humans is via animal reservoirs and occurs through two cycles: a classic rat–flea–rat cycle and a peridomestic animal cycle, which can involve other mammals such as cats, opossums, and dogs.^{1,2} In these latter mammals there is serological and molecular evidence that *R. typhi* tends to be seasonal.²

In recent years, several cases have been reported in the Mediterranean area.^{3,4} Symptoms of MT are relatively non-specific and can mimic those of other infectious diseases, thus it is often unrecognized and under-reported. The most common clinical features of MT include the ‘classic triad’ of fever, headache, and rash.⁴ The clinical presentation is normally mild, but the disease

can be severe and even fatal. The severity of MT has been related to age, race, and delayed diagnosis. The mortality rate increases with aging, and the severity of infection is due to hepatic and renal dysfunction, central nervous system abnormalities, and pulmonary compromise.⁴ In Italy, MT was the most widespread rickettsiosis during World War II, especially in Sicily, from where other cases were reported in the late 1980s.⁵ We report herein a case of MT occurring in Calabria, where this illness has not been observed before.

2. Case report

In April 2013, a 75-year-old woman presented to the emergency unit with headache, tremors, difficulty speaking, a skin rash, and fever. The headache had started with the fever (up to 39.5 °C) in the preceding 5 days. Neck pain, visual complaints, respiratory symptoms, and arthralgia were absent. She reported no recent travel or eating unpasteurized food products. Five days prior to her admission to the emergency unit she had been evaluated by her general practitioner, who presumed a bacterial illness and

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prescribed oral acetaminophen (1 g three times daily) and intramuscular cefepime (1 g twice daily). After 4 days of illness at home, the patient's condition appeared to improve, with a slight decrease in body temperature and a reduction in the headache; this was probably due to the acetaminophen effect. The next day she was clinically worse, with a higher fever, tremors, and a skin rash, thus she was hospitalized in the emergency unit.

Her medical history included gastroesophageal reflux disease, hypertension, and depression, for which she was treated regularly with proper pharmacological therapy. A physical examination revealed fever of 39.2 °C, blood pressure of 100/60 mmHg, heart rate of 98 beats/min, respiratory rate of 16 breaths/min, and oxygen saturation of 95% on room air. She appeared confused and there was an erythematous macular rash on her trunk, arms, legs, and abdomen (Figure 1).

Laboratory parameters showed hyperglycaemia (418 mg/dl), an increased number of white blood cells ($14.5 \times 10^9/l$) and serum creatinine (4.1 mg/dl), a decreased number of platelets ($37 \times 10^9/l$), normal haemoglobin level (15.2 g/dl), and a moderate increase in aminotransferases (alanine aminotransferase 64 IU/l and aspartate aminotransferase 158 IU/l). On the same day, following the appearance of hypotension (80/40 mmHg), the patient was moved to the infectious diseases unit for suspected sepsis. She was then treated with intravenous (IV) administration of dopamine (up to 15 ml/h) and meropenem (500 mg twice daily) plus levofloxacin (750 mg every 48 h). Due to respiratory problems, she was moved again, on the same day, from the infectious diseases unit to the intensive care unit.

Serological tests for viral hepatitis, HIV, cytomegalovirus, and Epstein–Barr virus were undertaken, and all results were negative.



Figure 1. (A) Diffuse morbilliform rash involving the abdomen. (B) Cutaneous morbilliform/petechial rash on the arm of a patient infected with *Rickettsia typhi*.

Blood and urine samples were also negative on Gram staining and culture. A head computed tomography scan and chest X-rays were negative for lesions suggestive of focal infection or leukaemia and other malignancies. Abdominal ultrasound showed only a small liver enlargement. On day 2, the patient had persistent hyperpyrexia (up to 40 °C).

On day 3, a careful re-visitation of the patient's history revealed that she was frequently exposed to ticks and fleas through contact with several household cats and dogs. This information, together with the symptoms and the skin macular rash that spared the palms of the hands and soles of the feet, suggested a diagnosis of MT. On the same day, serology tests for spotted fever group and typhus group rickettsial infections were performed; both were negative, and the antibiotic therapy was switched to tigecycline (100 mg IV) as a loading dose, followed by 50 mg IV twice daily for 7 days. A complete resolution of fever was observed within a few hours (8 h).

On day 8, blood and urine culture tests were again negative. On day 10, septic shock and multiple organ failure syndrome were resolved. Ten days after admission, an IgM assay for *R. typhi* was positive with a titration of 1:256, confirming the diagnosis of MT. The antibody titre was evaluated by indirect immunofluorescence assay (IFA) using a commercial kit, which includes positive and negative controls (Focus Diagnostics, Inc., Cypress, CA, USA).

3. Discussion

Clusters of murine typhus (MT) infection in Texas and California, as well as in travellers from Mediterranean areas, have been reported recently, reminding us of the potential impact of this illness on public health.^{1,3} Our case report suggests that this infection could be an emerging disease in a non-endemic area where the rat population density is low. The replacement of the classic cycle of *R. typhi* with others involving different hosts, such as the Virginia opossum (*Didelphis virginiana*), cat flea (*Ctenocephalides felis*), and dogs, likely contribute to explain our observation.^{1,2} Indeed, our patient was exposed to ticks and fleas through contact with cats and dogs. However, a history of flea exposure and bites is usually not recalled by patients.

Laboratory abnormalities may include moderately elevated hepatic aminotransferases and leukopenia, although the latter was not evident in the present case. The diagnosis is generally based on serological methods, demonstrating an at least four-fold increase in IgG/IgM specific to typhus group antibody titres from the acute to the convalescent phase.² We used the indirect IFA technique, which shows a slight and variable cross-reactivity with other rickettsial species, especially *Rickettsia felis*. We excluded *R. felis* based on clinical evidence: there was no eschar, and a rash sparing the palms and soles is more closely related to *R. typhi*. Discrimination between the two species requires analysis by PCR, which is not available for routine use in many laboratories, as reported in patients from the USA (Texas), Mexico, France, and Brazil.¹

Finally, treatment should be timely and started before the results of serological tests are available in order to avoid severe complications and death. Thus, for an early diagnosis, clinicians must rely on the scrupulous observation of significant signs and symptoms.

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