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Case report

Severe interstitial pneumonia due to murine typhus in a patient returning from Bali

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A B S T R A C T

Murine typhus has been increasingly reported as a cause of fever in returning travelers from Southeast Asia. We report a case of a previously healthy traveler returning from Bali with an non-specific febrile illness which quickly progressed to a severe form of interstitial pneumonia. After a careful epidemiological evaluation and laboratory analysis, murine typhus was diagnosed.

Due to their non-specific presentations, most febrile illnesses in returning travelers are hard to diagnose clinically. While many of them are self-limited, others like malaria, dengue and typhoid fever require specific treatment due to their complications and must be quickly excluded. Some diseases like murine typhus, require a high level of suspicion and careful epidemiologic evaluation to be diagnosed, as sometimes they may present in severe forms. Awareness is important, especially in countries where the disease is not endemic and may be not included in the differential diagnosis. We draw attention to murine typhus as an important differential diagnosis in travelers returning from Southeast Asia and to its uncommon, but important, pulmonary complications.

Introduction

Murine typhus is a systemic disease caused by *Rickettsia typhi*, a Typhus group bacteria from the *Rickettsiaceae* family, transmitted to the human by the rat flea *Xenopsilla cheopsis* [1]. The reservoirs are two murine rodents known as the brown (*Rattus norvegicus*) and black (*Rattus rattus*) rat [2]. As the reservoirs and vector are common in most countries, the disease is spread worldwide, especially in temperate climates and coastal/harbor areas, depending on rodent control programs and hygiene standards. Murine typhus is mainly characterized by a mild self-limited syndrome with fever, myalgia and headache, although some severe manifestations as pneumonitis, hepatitis and meningoencephalitis may also occur.

In Portugal, murine typhus incidence is unknown [3]. It may be a relevant differential diagnosis due to potential complications, especially in the traveler presenting with fever coming from an endemic country such as those in Southeast Asia. We present a case of a traveler returning from Bali, an Indonesian island in the Pacific Ocean, with a non-specific febrile illness complicated by severe interstitial pneumonia.

Clinical report

A 38 year-old previously healthy woman returned from a 2 week-long trip to Bali. She had no pre travel consultation and did not take any malaria prophylaxis. During her stay, she travelled around rural areas of the island where she had close contact with people living in poor water and sanitation conditions. She mentioned seeing rats around the accommodation and recalled several mosquito bites, apart from sporadic contact with dogs and cats, with no scratching or biting episodes. She returned to Portugal asymptomatic, but a week after arrival she presented to the emergency department complaining of fever, chills, malaise, myalgia and conjunctival congestion. Her initial blood tests

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Table 1
Blood analysis results. Legend: ALT – alanine aminotransferase; AP – Alcaline Phosphatase; AST – aspartate aminotransferase; B – Bilirrubin; DB – direct bilirrubina; CK – creatinine kinase; CRP – C-reactive protein; Eos – Eosinophyles; gGT – Gamma glutamyl transpeptidase; Hb – Hemoglobin; Leuc. – Leucocytes; LDH – Lactate desidrogenase; Lym – Lymphocytes; Neu – Neutrophiles; PLT – Platelets; SCr – serum creatinine; U – urea.

	Range	Day 1	Day 3	Day 4	Day 5	Day 7	Day 9	Day 11	Day 23
Hb (g/dL)	12–16	12.9	13.1	12.2	13.0	11.5	9.8	11.9	11.2
Leuc (*10^9/uL)	4–11	4.850	4.970	6.540	5.59	15.10	13.12	12.29	9.03
Neu(%)	53-69	65.4	79.6	84.5	78.4	62.4	39.5	39.5	25.4
Lym(&)	22–36	24.1	7.7	12.2	14.1	29.2	41.5	41.4	62.4
Eos(%)	0.6 – 4.6	0.0	0.0	0.0	0.0	0.1	1.0	1.2	1.0
PLT(*10^9/uL)	150–400	265	135	69	51	60	193	403	636
ALT/AST (U/L)	(10–31)	36/53	116/128	191/237	328/403	169/118	111/89	139/105	67/36
AP/gGT (U/L)	(7–32/30 – 120)	109/25	167/73	175/80	187/91	204/69	349/122	445/212	155/69
B/DB (mg/dL)	(< 1.2/ < 0.4)	0.42/0.11	0.79/0.22	1.03/0.4	0.9/0.23	1.38/0.52	0.95/0.24	0.86/0.26	1.00/0.21
LDH (U/L)	135–255	297	351	507	677				
CK (U/L)	10–149	110	95	105	127				
SCr (mg/dL)	0.51 – 0.95	0.74	0.66	0.61	0.53	0.51	0.51	0.47	0.6
U (mg/dL)	10–50	32	30	19	17	31	29	19	25
CRP (mg/L)	< 3.0	20.9	56.7	102	193	256	87.1	23.1	

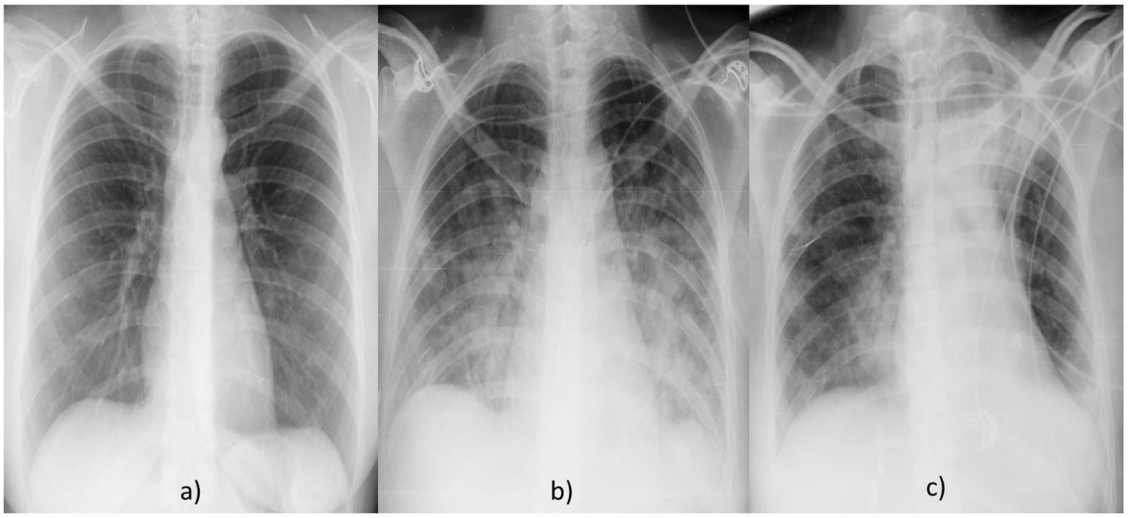

Fig. 1. a) Chest X-ray on the 1st day of fever; b) Chest X-ray on the 4th day of fever and on admission to the ICU; c) Chest X ray on the 7th day of antimicrobial.

(Table 1-Day 1) showed unremarkable changes. Chest X-Ray (Fig. 1a) was normal. Initial investigations for malaria and dengue were negative and she was discharged home with symptomatic treatment with acetaminophen. Forty-eight hours later the patient was re-evaluated in ambulatory and fever persisted, along with malaise and myalgia. Her general condition was good and physical examination was normal.

At this point, her blood tests presented relative neutrophilia, elevated hepatic aminotransferases and elevated LDH, with mildly increased C-reactive protein (Table 1-Day 3). Chest X-ray and abdominal ultrasonography had no abnormalities. Two blood samples were collected for culture in aerobic conditions and a first serologic screen was requested (Table 2). The patient was admitted to the Infectious Diseases Ward for observation.

On the 1st day after admission (day 4 of symptoms) her clinical and analytical condition deteriorated with shortness of breath (respiratory rate of 32/minute, SatO2 90–92% on room air), hypotension (70–80/30–40 mmHg), headache, nausea and a faint, transient, macular rash in the abdomen, trunk and arms. She looked acutely ill. Arterial blood gas examination revealed a respiratory alkalosis with a pO2/FiO2 ratio of 327 and hyperlactacidemia (2.88 mg/dL). Her chest X-ray (Fig. 1b) revealed a bilateral interstitial infiltrate in the lung parenchyma suggestive of interstitial pneumonia.

The patient was admitted to the Intensive Care Unit (ICU) with volume expansion with Intravenous (IV) fluids, IV ceftriaxone (2 g per day), IV doxycycline (100 mg twice daily) and oseltamivir (75 mg twice daily). Oxygen support was delivered by high flux nasal prongs. At this point, new microbiological exams were requested (Table 2).

While in the ICU, the patient condition improved progressively, with no need of invasive ventilation or vasopressive support. Oliguria was reverted. There was a transient decrease in hemoglobin and worsening thrombocytopenia and coagulopathy, which recovered spontaneously. The patient became afebrile by the 4th day of antimicrobial, was discharged from ICU on day 5 and fully recovered by the 7th day of antimicrobials (10th day of disease). Ceftriaxone was given for 8 days, while doxycycline was given for a total of 14 days (7 days by IV route and 7 days by oral route).

At discharge from the hospital (day 13), the patient was asymptomatic. Chest X-ray (Fig. 1c) confirmed resolution of the pulmonary infiltrates. A molecular diagnostic test using polymerase chain reaction (PCR) for *Rickettsia spp*. subgroup Typhus was later found to be positive. All other microbiological exams were negative.

To confirm the diagnosis of *R. typhi* infection, serum samples from acute (day 4 of disease) and convalescent (2 weeks after discharge) phases were sent to the Center for Vectors and Infectious Disease Research (*Centro de Estudos de Vectores e Doenças Infecciosas* – CEVDI) of the National Institute of Health in Águas de Moura, Setúbal, Portugal, were they were tested by immunofluorescence assay using a commercial Rickettsia IFA Substrate Slide kit® (Focus Diagnostics, USA). Seroconversion in two consecutive samples of the patient was demonstrated by the appearance of antibodies levels in second sample with

Table 2
Microbiological results. Legend: Ab – Antibodies; Ag – Antigen; CMV – Cytomegalovirus; EBV – Epstein-Barr Virus; NAAT – Nucleic Acid Amplification Test; NS1 – non-structural protein 1; SG1–Serogroup 1; TPPA – *Treponema pallidum* particle agglutination test.

	Product	Day 1	Day 3	Day 4	Day 5	Day 28
Blood cultures (each pair)	Blood	Negative	Negative	Negative		
Urine culture	Urine		Negative			
Plasmodium test (antigen and thin smear)	Blood	Negative	Negative	Negative		
Dengue test (NS1 + Ab)	Blood	Negative	Negative	Negative		
Dengue NAAT	Blood	Negative	Negative			
Chikungunya NAAT	Blood	Negative				
Influenza A/B NAAT	Nasal swab		Negative			
Leptospira spp. NAAT	Blood		Negative			
Leptospira spp. NAAT	Urine		Negative			
Heterophile Ab	Blood			Negative		
CMV Ab	Blood		IgG +			
EBV Ab	Blood		VCA IgM + Early IgG − EBNA IgG + VCA IgG+			
Coxiella burnetii Ab	Blood		Negative			
Rickettsia conorii Ab	Blood				Negative	
Borrelia spp. Ab	Blood				Negative	
Toxoplasma spp. Ab	Blood				Negative	
Treponemic test (TPPA)	Blood				Negative	
Mycoplasma pneumoniae	Blood			Negative		
Chlamydophila pneumoniae	Blood			Negative		
Legionella pneumophila SG1 Ag	Urine			Negative		
S. pneumoniae Ag	Urine			Negative		
Hepatitis E NAAT	Blood			Negative		
Rickettsia spp. NAAT	Blood				Positive for *Rickettsia* spp. group typhus Negative for *Rickettsia* spp. spotted fever group	
Rickettsia typhi NAAT	Blood			Positive		
Rickettsia typhi Ab	Blood			Negative		IgM 1:2048 IgG 1:4096

endpoint titers for IgM of 2048 and for IgG of 4096.

Molecular detection for rickettsial DNA was performed in buffy coat specimen. Briefly, DNA was extracted using the commercial QIAamp One-For-All Nucleic Acid Kit® (Qiagen, Hilden, Germany) according to the manufacturer's recommendations. Nested – PCR was performed targeting citrate synthase (gltA) gene fragment for *Rickettsia* spp. as previously described [4]. Positive amplicons were sequence and edited by using Lasergene software (DNASTAR, Madison, WI, USA).

Sequence characterization, performed by BLAST analysis, revealed that the our sequence was closest to the corresponding sequence of *R. typhi*, showing 99% (391/392) bp identity with gltA of *R. typhi* sequences deposit in GeneBank with accessions numbers CP003398, AE017197, U59714.

Conclusion

In Portugal, the only rickettsial disease of public health concern with mandatory reporting is Mediterranean spotted fever (MSF) caused by *R. conorii*. Murine typhus was common in Portugal in the 1950′s but its incidence declined over time and there have been no reported cases of murine typhus since 1998 [5]. Since murine typhus does not require a mandatory report to public health authorities in Portugal, under-reporting may occur.

Outside Europe, murine typhus is reported in Southeast Asia and Central and South America, as well as many other countries where sanitary conditions are still improving. There are no consistent data from the African continent [6,7]. Although malaria, dengue and typhoid fever lead as the main causes of fever in residents of southeast Asia, it is well known that rickettsia infections follow as frequent causes in that population, especially in rural areas and within refugee population [8,9].

In the traveler returning from endemic areas and presenting with fever, murine typhus should be considered in the differential diagnosis, along with malaria, typhoid fever, leptospirosis, dengue, chikungunya and other arboviruses. Contact with animals and visits to rural areas are important epidemiological clues that may help in the diagnosis, as well as knowledge on local disease patterns. In recent years, a few case reports of murine typhus in travelers returning from Bali increased its relevance as a differential diagnosis, although murine typhus is still very rarely reported [10–12].

While asymptomatic in up to a third, the disease manifests in 60–70% of the cases as a mild febrile illness with musculoskeletal pain and headache after a 1–2 weeks incubation period. Due to its non-specific presentation, diagnosis relies on high index of clinical suspicion and laboratory confirmation. A macular or maculopapular rash of the trunk and extremities may also develop on the 5th day of fever, usually sparing palms and soles, the latter being a useful clinical feature to distinguish murine typhus from spotted fever rickettsiosis. Murine typhus may uncommonly (10%) present with organ-specific lesion such as pneumonitis, hepatitis, meningoencephalitis, renal failure and septic shock.

As seen in our patient, a recent review suggests that pulmonary involvement in murine typhus may be more common than it was thought, as there was a prevalence of radiological abnormalities in 16.7% in whom a chest radiograph was performed. Most abnormalities consisted in bilateral or unilateral interstitial infiltrates. The pulmonary changes in murine typhus may be associated with damaged pulmonary microcirculation, but reports on respiratory distress or failure was only found in 7 patients, 2 of which presented with an acute respiratory distress syndrome (ARDS), with a fatal outcome. Most of the severe cases with pulmonary manifestations originated in Asia, which may reveal a pattern of geographic distribution of different pathophysiological manifestations [13].

Due to its non-specific presentation of fever, malaise and myalgia, it may be misidentified as an influenza-like illness, or, if the epidemiologic context is compatible, as an non-specific febrile illness in the

returning traveler after excluding malaria and dengue in the emergency department. However, even when considered as a diagnosis, laboratory resources for the confirmation of murine typhus are not widely available.

This case is the first identified case of murine typhus in Portugal since 1998. Mortality of murine typhus ranges from 0 to 1%, but several risk such as an older age, hematologic diseases and delays in the diagnosis and antimicrobial treatment may contribute for a worse prognosis. The main question that remains to be answered is why a previously non-pregnant healthy woman, without smoking habits or comorbidities, developed such an atypical and severe manifestation of the disease. Some reasons for this presentation could have been a high inoculum or a specific southeast strain of *R. typhi.* The delay in adequate antimicrobial treatment and aggressive IV fluid therapy for hypotension, may have also contributed for the ARDS. Whether this was an isolated event or other reasons exist, should be answered in future clinical or epidemiological studies.

As Southeast Asia grows as a prominent tourist destination for a variety of urban and ecotourism activities that have the potential risk of exposure to *Rickettsia* spp. vectors, it is expected that the incidence of imported rickettsial diseases will increase in the coming years [6]. Recently, southeast Asia ranked as the 2nd most common destination visited by ill returned travelers [14]. When a diagnosis was made (up to 75%), the most common causes of febrile illnesses in travelers returning from southeast Asia included malaria, dengue and typhoid fever, justifying an accurate exclusion of these infections, such as what was performed in this case. Rickettsial infections are also frequent identifiable causes of systemic febrile illness in returned travelers, although these are mainly caused by spotted fever group rickettsia (72%) [15–17]. This highlights the importance of the knowledge on the world epidemiology of infectious diseases when approaching the returned traveler with fever.

Although endemic in Southeast Asia, murine typhus is rarely diagnosed in the returning traveler, mainly due to an non-specific self-limited presentation and lack of diagnostic capacities of most hospitals. Even though a benign presentation is the rule, murine typhus may also complicate with organ failure and lead to death, especially if correct treatment is not started. This highlights the importance of the knowledge on the world epidemiology of infectious diseases when approaching the returned traveler with fever.

Conflicts of interest

None.

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Declaration of informed consent

A declaration of informed consent for publication has been obtained from the patient whose details are described in the manuscript.

Authors' contributions

LM, FC and JA took part in the clinical management of the patient and wrote the manuscript. ACC, AS and LS took part in the clinical management of the patient and reviewed the manuscript. JSS and RS collaborated in molecular biology techniques. RS performed the serology and molecular diagnosis tests and the sequence of the *R. typhi* and wrote the lab section. All authors read and approved the final manuscript.

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