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Case Report

Murine typhus presenting with status epilepticus

Humaira Shafi[a,*], Louie Galang Hipolito[b]

[a] Department of General Medicine, Department of Infectious Diseases, Changi General Hospital, 2 Simei Street 3, Singapore, 529889, Singapore
[b] Department of General Medicine, Changi General Hospital, 2 Simei Street 3, Singapore, 529889, Singapore

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ABSTRACT

Patients with rickettsial infection usually present with a febrile illness, headache, arthromyalgia and various biochemical abnormalities. Neurologic involvement is rare in murine typhus. Here, we report a case of a patient who presented with status epilepticus secondary to *Rickettsia typhi* infection.

Introduction

Murine typhus (MT) is a zoonotic flea-borne infectious disease caused by *Rickettsia typhi.* It is primarily transmitted by the rat flea *Xenopsylla cheopis,* also known as oriental rat flea. Humans are infected by inoculation of infective flea feces in bite wounds. The actual incidence of murine typhus is difficult to establish since infection can be mild and self-limited. Murine typhus is typically a mild illness with an incubation period from 8 to 16 days. The onset of illness is usually relatively abrupt, with nonspecific symptoms like fever, headache, chills and myalgia followed by rash which occurs in some patients near the end of the first week of illness. Neurologic manifestations have also been described. Here, we present a case of an immigrant construction worker in Singapore who presented with status epilepticus.

Case report

A 31-year-old Bangladeshi male, presented to the emergency room (ER) of another tertiary hospital with 10-day history of fever, myalgia and headache. He had no past medical history, was not taking any medications and no drug allergies were reported. He was born in Bangladesh and worked as a carpenter in Singapore. He lived in a shared dormitory with poor environmental cleanliness. He visited Bangladesh five months prior to current illness. He drank alcohol socially. Physical exam revealed an alert patient with no focal deficits. His temperature was 37.4 °C. The remaining exam results were unremarkable. Investigations showed an ALT 121 U/L, AST 91 U/L. Full blood count, renal panel and chest x-ray were unremarkable. Urine dipstick showed 1+ proteinuria, 2+ blood, 1+ leukocyte. He was discharged with a diagnosis of viral fever and was prescribed diclofenac, omeprazole and acetaminophen/orphenadrine with return advice.

Five days later he was admitted to our hospital with sudden onset of generalized tonic-clonic seizure at the airport while waiting to board the plane. This was witnessed by bystanders, followed by another seizure which was witnessed by the ambulance staff and haloperidol was given. Subsequently upon arrival to ER, another seizure occurred, which was aborted with intravenous (IV) diazepam followed by initiation of IV levetiracetam with good response. Physical exam showed temperature of 36.1 °C, blood pressure 107/73 and heart rate of 128 beats/min. Glasgow Coma Scale (GCS) upon admission was E4M4V3. There were no signs of meningeal irritation on exam. Remaining examination results were unremarkable. Initial work up showed white blood cell count of $15.4 \times 10^{\times 3}$/μL, platelet count of $61 \times 10^{\times 3}$/μL, serum lactate 8.31 mmol/L, urea of 20 mmol/L, serum creatinine 612 μmol/L, serum bicarbonate of 5 mmol/L (Table 1) and arterial blood pH 7.19. A non-contrasted computerized tomography (CT) of the brain was unremarkable. He was admitted to the intensive care unit (ICU) with status epilepticus secondary to meningoencephalitis and acute kidney injury (AKI).

Lumbar puncture showed cerebrospinal fluid (CSF) cell count of 126 cells/mm^3, 80% neutrophils, protein 0.99 gm/L, glucose

* Corresponding author at: Changi General Hospital, 2 Simei Street 3, Singapore 529889, Singapore.
E-mail address: shafi.humaira@singhealth.com.sg (H. Shafi).

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Table 1
LAB DATA.

	Investigations from other tertiary hospital	On admission to our hospital	Day 10
Urea	2.3 mmol/L	20 mmol/L	17 mmol/L
Creatinine	100 μmol/L	612 μmol/L	112 μmol/L
Bicarbonate	23 mmol/L	5 mmol/L	25 mmol/L
Platelet count	$196 \times 10^{\times 3}/\mu L$	$61 \times 10^{\times 3}/\mu L$	$350 \times 10^{\times 3}/\mu L$
WBC count	$7.8 \times 10^{\times 3}/\mu L$	$15.4 \times 10^{\times 3}/\mu L$	$7.8 \times 10^{\times 3}/\mu L$
Hemoglobin	15.8 g/dL	17.4 g/dL	8.1 g/dL
AST	91 U/L	102 U/L	45 U/L
ALT	121 U/L	107 U/L	52 U/L
ALP	68 U/L	182 U/L	108 U/L
Total bilirubin	13 μmol/L	53.1 μmol/L	11.6 μmol/L
APTT/PT	–	40.2 s/12.4 s	21.9 s/10.9 s
CRP	–	416 mg/L	6.1 mg/L
Procalcitonin	–	19.52 μg/L	0.20 μg/L

3.1 mmol/L. CSF cytology demonstrated a paucicellular specimen with rare mononuclear cells, which was negative for AFB and fungal cultures. CSF meningitis/encephalitis PCR was negative for *Crypotococcus neoformans/gattii*, HSV1/2, CMV, VZV, HHV-6, enterovirus and human parechovirus. Cultures of blood, urine and CSF were negative. Leptospira IgM was negative. Blood leptospira PCR was negative. Malarial parasite smear was negative. Dengue, Chikungunya and hepatitis A/B/C serology was unremarkable.

The patient was empirically started on intravenous ceftriaxone, ampicillin, vancomycin and acyclovir. Continuous renal replacement therapy (CRRT) was initiated for AKI. Levetiracetam was prescribed for seizures. On ICU day 3, GCS was noted to be 3. He was intubated for airway protection. A repeat brain CT reported possible midbrain stroke, however brain MRI did not show any acute infarct. MRA was unremarkable. Intravenous doxycycline was added. Neurological status improved over the course of next 3–5 days and patient was extubated five days later. Simultaneous improvement was noted in renal functions and platelet counts (Table 1). Rickettsia serology showed a titer of 1024 for R. *typhi* Ig Total IF. *Rickettsia rickettsii* and *Orentia tsutsugamushi* titers were <128. The patient made a full recovery and was subsequently lost to follow up.

Discussion

Murine typhus, also called endemic typhus or flea-borne typhus is a zoonotic disease which has been described worldwide and is common in Southeast Asia. It is caused by an obligate intracellular Gram-negative bacteria *R. typhi* (Carr et al. 2014). Rodents and arthropods serve as a natural reservoir (Chang et al. 2017). It is primarily transmitted by the infected oriental rat flea *X. cheopis*. Humans are infected when feces from the rat flea is inoculated into human skin at the site of flea bite. The organism can also be inhaled from an environment contaminated with rat flea feces. Another proposed route of transmission predominantly involves cats, opossums and their fleas *Ctenocephalides felis*(Simon et al. 2011).

Murine typhus has protean manifestations. Illness can range from an undifferentiated febrile syndrome to life threatening illness causing pneumonia, respiratory failure, acute renal failure, acute hepatitis, meningitis or meningoencephalitis, cranial nerve palsies, coagulopathy, disseminated intravascular coagulation (DIC) and death(Simon et al., 2011; Moy and Ooi, 2015; X-ray, 2010).

Neurological manifestations have been described both in children (Galanakis et al., 2002) and in adults. CSF studies usually are consistent with aseptic meningitis. Papilledema, cranial nerve palsies, focal neurologic deficits and seizures have been reported (Moy and Ooi 2015; Simon et al., 2011). Meningoencephalitis, behavior and memory disturbances as delayed consequences have been published, although recovery occurs (Silpapojakul et al., 1991; Masalha et al., 1998; Moy and Ooi, 2015; Simon et al., 2011; Massung et al., 2001; Dittrich et al., 2015; Samra et al., 1989; Carr et al., 2014). Status epilepticus has been described in Japanese spotted fever, which is caused by *Rickettsia japonica* (Nakata et al., 2012) as well as in MT with fatality (Stephens et al., 2018).

In our case, illness started with fever, headache and myalgias which mimicked a viral illness. This is not unusual as tropical diseases share overlapping clinical features making clinical diagnosis challenging. Also, tedious turnaround time of available serologies does not offer much help in establishing a real-time diagnosis. As such, the diagnosis is usually established retrospectively as in this case. The patient's rickettsial serology results were only available on hospital day 14, when discharge planning was already in progress.

We hypothesize that his source of infection was likely rodent exposure at occupational sites where he worked as a carpenter and perhaps also contributed by crowded living situation in a shared dormitory with poor environmental cleanliness. The patient did notice rat droppings in the dormitory. Often, exposure can be difficult to illicit.

Koh et al. reported MT in 6 migrant Indian and Bangladeshi workers within a period of 3 months in Singapore but no neurologic features were noted except confusion in one case (Loh et al., 1996). Similarly, Ong et al reported MT in both local and migrant worker populations in Singapore in 2001(Ong et al., 2001). Headache was present in 29% of the study population, but no other CNS manifestations were recorded.

The diagnosis of MT requires a high clinical suspicion, knowledge of local prevalence of disease and epidemiological risk factors. Admittedly the exposure history can be difficult to elicit when the patient is critically ill. Diagnosis can be confirmed serologically by identifying a seroconversion or four-fold rise in the titer of patient's group-specific antibodies against rickettsial agents utilizing an indirect fluorescent antibody (IFA) or enzyme-linked immunosorbent assay (ELISA) and via polymerase chain reaction (PCR)-based tests.

The preferred treatment option is doxycycline (Gikas et al., 2004; Howard and Fergie 2018). Alternatives include chloramphenicol, ciprofloxacin and azithromycin, however these regimens are associated with longer duration of fever and frequent relapse. In a recently published randomized trial from Laos, 3-day regimen of azithromycin was shown to be inferior where it was compared with 3- and 7-days of doxycycline and was associated with longer duration of fever, area under the time-temperature curve and treatment failure (Newton et al. 2019). Ciprofloxacin is to be used as a last option as evidence is scanty and it has the least amount of experience to support responsible recommendations (Strand and Strömberg 1990; Gikas et al., 2004). When using chloramphenicol

(Gikas et al., 2004), clinicians need to be mindful about the adverse effects of aplastic anemia.

In summary, MT remains an underrecognized and underreported illness. It can evolve into a life-threatening illness with significant morbidity. High clinical suspicion and prompt initiation of empiric doxycycline should be strongly considered in the appropriate clinical context.

Conflict of interest

The authors have no conflict of interest to declare.

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Ethical approval

Ethical approval was not required.

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