**CLINICAL VIGNETTE**

# Rickettsia Typhi – A Rare Cause of Meningismus

Usman Alam and Sabrina M. Tom, MD

***Background***

Murine typhus is an acute febrile illness caused by the flea-borne organism, Rickettsia typhi. Like other members of the Rickettsial family, R. typhi is an intracellular gram-negative bacterium that infects endothelial cells in mammalian hosts, most commonly cats and rats. Transmission of R. typhi to humans occurs through contact with vectors such as the cat flea (Ctenocephalides felis) or the rat flea (Xenopsylla cheopis). While there are other types of fleas that may transmit R. typhi, the rat flea is the most common. Consequently, cases of murine typhus worldwide typically occur in temperate and subtropical coastal regions where there is an abundant rat population.

In the United States, murine typhus infection is most commonly reported during the late summer in the states of California and Texas.[1–4] The true incidence of murine typhus, however, is not well established likely due to its often benign and nonspecific presentation. Despite the low mortality associated with murine typhus, early clinical suspicion and timely treatment of the disease can significantly decrease severity and duration of illness.

***Case Report***

A 24-year-old man without significant medical history presented to the ED with a moderate-to- severe headache for six days. He had come to the ED two days before with headache and was discharged with return precautions. His headache had been gradually worsening, was focused on the right side and was associated with neck stiffness, photophobia, nausea and fevers to 103 F at home. He denied confusion, vision changes, numbness or tingling, weakness, dizziness, or seizures. He also denied weight loss, arthralgias, myalgias, vomiting, abdominal pain, diarrhea, bloody stool, dysuria, hematuria, chest pain, dyspnea, or cough.

He denied sick contacts or recent travel. He had not been hiking or camping. He denied pets at home although reported seeing rodents and opossums near his house. He did not recall any bug bites. He was last sexually active with one female partner one month prior to presentation and endorsed consistently using barrier protection. He denied drug, tobacco use or significant alcohol use.

On examination, the patient had a temperature of 39.3 C, heart rate of 103 beats/min, respiratory rate of 20 breaths/min, blood pressure of 126/72 mmHg and oxygen saturation of 98% on room air. He had a normal neurologic exam but demonstrated nuchal rigidity and photophobia. The patient had not previously noticed, a diffuse, blanching, macular rash over his bilateral lower extremities that spared the soles of his feet. The remainder of his exam was normal.

CT brain was unremarkable. LP resulted 1 RBC, 0 WBC, glucose 57 (mg/dl), protein 49 (mg/dl). Laboratory evaluation was notable for thrombocytopenia to 113 x 1000/mm3, elevated AST 91 U/L and ALT 209 U/L. Chest x-ray and EKG were normal. Urinalysis was normal. Blood cultures were negative.

Ceftriaxone and acyclovir were started for empiric treatment of meningitis but were discontinued after two days. Infectious Disease was consulted and suggested that the patient's presentation was most consistent with an infection caused by Rickettsia typhi. The patient started doxycycline 100mg twice daily with improvement of his fevers, headache, neck mobility and appetite. His thrombocytopenia resolved but elevations of AST (251 U/L) and ALT (393 U/L) continued. A CT of the abdomen and pelvis was negative. A CSF meningitis/ encephalitis panel was negative, including testing for Cryptococcus and West Nile Virus. Other negative tests included serological studies for HIV, RPR, CMV IgM, Hepatitis viruses, C. Burnetii, Brucella, and Rickettsia.

The patient was discharged on the fifth day of hospitalization after no fevers were observed for 24 hours. Although initial Rickettsia serologies were negative, Infectious Disease maintained that Rickettsia typhi was the most likely diagnosis, and the patient was continued for a total 11-day course of doxycycline. The patient's transaminases normalized, and he declined repeat serological testing for Rickettsia given that all of his symptoms had resolved by his follow-up appointment.

***Discussion***

The clinical presentation of Rickettsia typhi infection, also known as murine typhus, can be described as variable and nonspecific. Based on clinical descriptions reported worldwide, the most common presenting signs and symptoms of murine typhus include fever (98-100%), headache (41-90%), rash (20-80%), arthralgia (40-77%), hepatomegaly (24-29%), nausea/ vomiting (3-48%) and cough (15-40%)[1,4–6]. Fever generally lasts 3-7 days. Rash is seen in approximately 18% of patients on presentation, but up to 80% of patients may develop a non-

pruritic macular or maculopapular rash one week after the onset of fever.[5,6] The rash is most commonly located on the trunk but can be present on the extremities as well.[5]

While the presence of headache and fever are common, meningismus or meningeal findings are reported as rare.[7] CNS complications, when present, are often a late manifestation of the disease (10 days to 3 weeks from onset of fever) and may present as meningitis or encephalitis with a stiff neck, headache and fever,[5,8] or confusion.[9] Rarely, patients can develop more focal CNS abnormalities including facial paralysis, sensorineural hearing loss, ataxia, and seizures.[9–11]

Although the mortality rate of murine typhus is low, both with and without antibiotic treatment (1% and 4%, respectively), other serious complications have been reported. Cases of splenic rupture secondary to murine typhus have been documented in patients who present with longstanding fever and abdominal pain.[12] One case series described cases of acute renal failure secondary to acute infection of murine typhus.[13] Other rare reported complications include intraretinal hemorrhage and respiratory failure requiring intubation.[14,15] One series suggested a higher rate of complications in patients with increased age, prior renal dysfunction, or those who were treated with sulfa antibiotics.[7]

Laboratory findings of leukopenia (18-40%) and thrombocytopenia (19-48%) are commonly associated with murine typhus.[7] An elevated erythrocyte sedimentation rate is seen in 59-89% of patients.[7] Aspartate aminotransferase and alanine aminotransferase are also frequently elevated in the viral hepatitis range (67-90% and 67-99%, respectively).[5–7] In patients with suspected CNS involvement, CSF findings are often reflective of aseptic meningitis. These CSF findings are generally normal range glucose, normal or elevated protein levels, and elevated white blood cells (ranging from 10-650 cells/mm$^3$) with lymphocytes as the major cell type.[9,16] Interestingly, our patient demonstrated meningismus, but CSF findings were not consistent with meningitis.

A diagnosis of murine typhus can only be definitively made with an indirect immunofluorescence assay (IFA). Despite IFA being considered the gold standard for diagnosis, it is rarely diagnostic during the acute phase of infection. Rather, IFA titers serve to be more reliable diagnostic markers by 15 days after onset of illness.[7] Given its difficulty and impracticality, culture is often not attempted. Polymerase chain reaction can also be used to amplify R. typhi nuclear genes, but this method has not been thoroughly evaluated for sensitivity or specificity, and it is not widely available in clinical laboratories. For these reasons, diagnosis of murine typhus is based largely on clinical suspicion, and treatment should not be delayed while awaiting laboratory results.

Many retrospective studies have shown that the most effective treatment of murine typhus is doxycycline.[4–7] On average, patients are afebrile within 3 days of initiation of treatment.[17] Although one case series described a single dose of doxycycline resulting in 80% efficacy, it is recommended to continue treatment either until 2-3 days after fever resolves or a 7-10 day total course.[18,19] Corticosteroids are occasionally used to address CNS sequelae of complicated infection, but no studies have validated their use.

Given the lack of rapid confirmatory serologic testing and nonspecific symptoms of presentation, the diagnosis of murine typhus remains a challenge. For patients with exposure in endemic regions, it is important to consider the diagnosis of murine typhus as a cause of persistent fever of unclear etiology, especially when other suggestive features such as headache and rash are present. Timely recognition and treatment is important for decreasing the duration and severity of disease, and treatment should be pursued when there is high clinical suspicion, even if initial serologic testing is negative.

## REFERENCES


1. **Civen R, Ngo V**. Murine typhus: an unrecognized suburban vectorborne disease. *Clin Infect Dis*. 2008 Mar 15;46(6):913-8. doi: 10.1086/527443. Review. PubMed PMID: 18260783.
2. **Abramowicz KF, Rood MP, Krueger L, Eremeeva ME**. Urban focus of Rickettsia typhi and Rickettsia felis in Los Angeles, California. *Vector Borne Zoonotic Dis*. 2011 Jul;11(7):979-84. doi: 10.1089/vbz.2010.0117. Epub 2010 Dec 13. PubMed PMID: 21142968.
3. **Eremeeva ME, Karpathy SE, Krueger L, Hayes EK, Williams AM, Zaldivar Y, Bennett S, Cummings R, Tilzer A, Velten RK, Kerr N, Dasch GA, Hu R**. Two pathogens and one disease: detection and identification of flea-borne Rickettsiae in areas endemic for murine typhus in California. *J Med Entomol*. 2012 Nov;49(6):1485-94. PubMed PMID: 23270180; PubMed Central PMCID: PMC5893996.
4. **Blanton LS, Vohra RF, Bouyer DH, Walker DH**. Reemergence of murine typhus in Galveston, Texas, USA, 2013. *Emerg Infect Dis*. 2015 Mar;21(3):484-6. doi: 10.3201/eid2103.140716. PubMed PMID: 25695758; PubMed Central PMCID: PMC4344263.
5. **Bernabeu-Wittel M, Pachón J, Alarcón A, López-Cortés LF, Viciana P, Jiménez-Mejías ME, Villanueva JL, Torronteras R, Caballero-Granado FJ**. Murine typhus as a common cause of fever of intermediate duration: a 17-year study in the south of Spain. *Arch Intern Med*. 1999 Apr 26;159(8):872-6. PubMed PMID: 10219934.
6. **Fergie JE, Purcell K, Wanat D**. Murine typhus in South Texas children. *Pediatr Infect Dis J*. 2000 Jun;19(6):535-8. PubMed PMID: 10877169.
7. **Whiteford SF, Taylor JP, Dumler JS**. Clinical, laboratory, and epidemiologic features of murine typhus in 97 Texas children. *Arch Pediatr Adolesc Med*. 2001 Mar;155(3):396-400. PubMed PMID: 11231808.
8. **Galanakis E, Gikas A, Bitsori M, Sbyrakis S**. Rickettsia typhi infection presenting as subacute meningitis. *J Child Neurol*. 2002 Feb;17(2):156-7. PubMed PMID: 11952082.

9. **Vallejo-Maroto I, García-Morillo S, Wittel MB, Stiefel P, Miranda M, Pamies E, Aparicio R, Carneado J**. Aseptic meningitis as a delayed neurologic complication of murine typhus. *Clin Microbiol Infect*. 2002 Dec;8(12):826-7. PubMed PMID: 12519359.
10. **Vander T, Medvedovsky M, Valdman S, Herishanu Y**. Facial paralysis and meningitis caused by Rickettsia typhi infection. *Scand J Infect Dis*. 2003;35(11-12):886-7. PubMed PMID: 14723370.
11. **Tsiachris D, Deutsch M, Vassilopoulos D, Zafiropoulou R, Archimandritis AJ**. Sensorineural hearing loss complicating severe rickettsial diseases: report of two cases. *J Infect*. 2008 Jan;56(1):74-6. Epub 2007 Nov 26. PubMed PMID: 18023483.
12. **McKelvey SD, Braidly PC, Stansby GP, Weir WR**. Spontaneous splenic rupture associated with murine typhus. *J Infect*. 1991 May;22(3):296-7. PubMed PMID: 2071915.
13. **Hernández Cabrera M, Angel-Moreno A, Santana E, Bolaños M, Francès A, Martín-Sánchez MS, Pérez-Arellano JL**. Murine typhus with renal involvement in Canary Islands, Spain. *Emerg Infect Dis*. 2004 Apr;10(4):740-3. Erratum in: *Emerg Infect Dis*. 2004 Jul;10(7):1353. *Emerg Infect Dis*. 2004 Sep;10(9):1708. PubMed PMID: 15200874; PubMed Central PMCID: PMC3323099.
14. **Bernabeu-Wittel M, Villanueva-Marcos JL, de Alarcón-González A, Pachón J**. Septic shock and multiorganic failure in murine typhus. *Eur J Clin Microbiol Infect Dis*. 1998 Feb;17(2):131-2. PubMed PMID: 9629982.
15. **Hudson HL, Thach AB, Lopez PF**. Retinal manifestations of acute murine typhus. *Int Ophthalmol*. 1997;21(3):121-6. Review. PubMed PMID: 9587827.
16. **Masalha R, Merkin-Zaborsky H, Matar M, Zirkin HJ, Wirguin I, Herishanu YO**. Murine typhus presenting as subacute meningoencephalitis. *J Neurol*. 1998 Oct;245(10):665-8. PubMed PMID: 9776466.
17. **Gikas A, Doukakis S, Pediaditis J, Kastanakis S, Manios A, Tselentis Y**. Comparison of the effectiveness of five different antibiotic regimens on infection with Rickettsia typhi: therapeutic data from 87 cases. *Am J Trop Med Hyg*. 2004 May;70(5):576-9. PubMed PMID: 15155995.
18. **Silpapojakul K, Chayakul P, Krisanapan S, Silpapojakul K**. Murine typhus in Thailand: clinical features, diagnosis and treatment. *Q J Med*. 1993 Jan;86(1):43-7. PubMed PMID: 8438048.
19. **Bennett JE, Dolin R, Blaser MJ**. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Elsevier; 2014.