

## CLINICAL VIGNETTE

# Murine Typhus: A diagnosis Often Overlooked

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### Case Report

A 54-year-old man with no prior medical history presented with 1 week of fevers, sweats, malaise, myalgias, nausea, dry cough, and headaches. His symptoms began with a headache, which was followed by fevers and sweats. He denied any sick contacts, travel history, joint pain, new rashes, neck pain, or visual changes. He denied eating any raw fish or shellfish, unpasteurized milk products, or wild game. He currently does not take any medications or herbal supplements. His family history was unremarkable. The patient is married and lives with his wife. Of note, she was hospitalized 3 weeks prior to his presentation for “pneumonia, low platelets, and liver problems.” Her symptoms improved enough and she was discharged home. The patient and his wife live in Santa Monica, and they have several cats and dogs. The pets live outside and have been known to bring dead rodents into the yard. He denied any direct exposure to these animals. He recalled having flea-bites in the past.

Physical examination was notable for bibasilar lung crackles and scattered petechiae on his lower extremities, but otherwise unremarkable. He was alert and oriented x 4, but slow with his responses. Vitals were significant for a temperature of 39.3°C, heart rate of 118, respiratory rate of 20 and oxygen saturation down to 86% on room air. He was placed on nasal cannula with improvement to 95% on 2L oxygen. Laboratory studies were markedly abnormal, revealing hyponatremia, elevated creatinine to 5.1 mg/dL, elevated liver function tests, hyperbilirubinemia, thrombocytopenia, leukocytosis with bandemia, and prolonged PTT. Imaging studies showed ground-glass opacifications bilaterally in the lower lobes on CT chest and mild hepatosplenomegaly on CT abdomen/pelvis.

The patient was empirically started on vancomycin and piperacillin/tazobactam for possible MRSA pneumonia and septic shock. He was also covered with levofloxacin for Legionella and oseltamivir for influenza. Infectious Diseases consult was obtained, and doxycycline was added to cover Rickettsia. His respiratory status improved. His renal failure, though, rapidly progressed to oliguria and required

initiation of hemodialysis on hospital day 2. Concomitantly, his hemoglobin declined, and blood smear indicated schistocytes concerning for hemolysis. Plasma exchange was performed for presumed thrombotic thrombocytopenic purpura. Serologies for Rickettsia typhus returned positive on day 5, and antibiotics were tapered to doxycycline only. Epstein-Barr Virus IgG was positive, but serologic tests for Q fever, Francisella, hantavirus, cytomegalovirus, syphilis, Bartonella, coccidioidomycosis, HIV, viral hepatitis, and Legionella urine antigen and influenza A and B nasal washings were subsequently all negative. Blood, sputum, and urine cultures were all negative. Renal function and platelet count had recovered significantly by the time of discharge on day 19. On his 2 week follow up in clinic, his renal function had continued to improve and his platelet count had returned to normal.

### Discussion

Incidence of *Rickettsia typhi* human infections is underreported and remains a public health concern<sup>1</sup>. Often referred to as “endemic/murine typhus” or “flea-borne typhus,” it is an intracellular gram-negative bacterium. It is transmitted through flea and tick bites from infected rodents, cats, dogs, and opossums. It is endemic in warm coastal areas around the world and is primarily found in the United States in California, Texas, and Hawaii. Most transmissions occurring through the cat flea (*Ctenocephalides felis*) have been associated with the opossum as host. In California, three to twenty-one cases of murine typhus have been reported annually between 1995 to 2008<sup>2</sup>. These statistics likely underestimate the true incidence of murine typhus as it is often underdiagnosed and can be misdiagnosed as a viral illness. Because fleas thrive in hot, dry environments, murine typhus cases often occur during the late summer and early fall months<sup>2</sup>. The clinical syndrome, called murine/endemic typhus, generally has an incubation period of 6-14 days, followed by symptoms of fever, maculopapular rash in 20-80%, headache, nausea, dry cough, thrombocytopenia in 19-60%, liver dysfunction, and renal insufficiency in

14-21%<sup>1,3</sup>. The rash is usually macular, but can also be maculopapular, papular, or petechial. These symptoms and clinical signs are often nonspecific, making it difficult to establish a definitive diagnosis without the availability of diagnostic testing. Other diagnoses to consider that may have similar presentations include insect-borne diseases [Rocky Mountain spotted fever (RMSF), babesiosis, and dengue], fungal infection (coccidioidomycosis), zoonotic infections (Q fever, tularemia, hantavirus, and leptospirosis), and viral infections (influenza, Epstein-Barr virus, and cytomegalovirus).

Serologic testing is the diagnostic test of choice, with immunofluorescence antibody as the “gold standard.” A four-fold or greater increase of IgG antibody titers specific to typhus group antigen confirms the diagnosis. Of note, typhus group antibodies may not always be present during the first week of infection, but are almost always present after two weeks<sup>4</sup>.

Risk factors for severe illness include male gender, older age, and presence of glucose-6-phosphate-dehydrogenase deficiency<sup>5,6</sup>. Mortality rate is extremely low, and while most cases are self-limiting, one case report attributed mortality to late diagnosis and delayed initiation of doxycycline<sup>5</sup>. In fact, odds ratio for major organ dysfunction and prolonged hospitalization of >10 days has been reported to be 1.2 and 1.4 per day of delayed doxycycline, respectively<sup>7</sup>. Serious complications arising from acute *Rickettsia typhi* infections include endocarditis, splenic rupture, and aseptic meningitis. Fortunately, there was suspicion of Rickettsial disease, and the patient’s clinical course likely improved with early initiation of doxycycline. Since serologic testing results may not be readily available to confirm a diagnosis, early initiation of doxycycline for suspected cases of murine typhus is imperative when there is a history of close animal contact. Cases of murine typhus often present as atypical pneumonia and are often empirically covered with macrolides, which have no activity against these organisms. Ciprofloxacin is active against non-RMSF *Rickettsia*. However, doxycycline remains the treatment of choice<sup>8</sup>.

### Conclusion

Murine typhus is often an underdiagnosed illness for a number of reasons. The clinical presentation overlaps with other causes of atypical pneumonia. Key features include prominent headache, high fever and failure to improve on macrolide therapy. Murine typhus had a peak incidence of 5000+ cases per year

in the 1940s with dramatic decreases in incidence to less than 100 per year attributed to improvement in public health measures against rodent infestations<sup>1</sup>. An improvement in public health likely decreased our vigilance for an illness that often lies dormant in our rodent and household pet population via fleas. Murine typhus should remain a public health concern for the foreseeable future as our population continues to grow, move into rural areas, and have close contact with animals. In summary, obtaining a careful history about exposure to fleas and sending serologic testing in a timely manner will help with making the diagnosis. However, one should not wait for serologic testing results to initiate treatment if murine typhus is suspected, treatment delay can lead to serious complications.

### REFERENCES

1. **Azad AF.** Epidemiology of murine typhus. *Annu Rev Entomol.* 1990;35:553-69. Review. PubMed PMID: 2105686.
2. **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.
3. **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 Sep;10(9):1708. *Emerg Infect Dis.* 2004 Jul;10(7):1353. PubMed PMID: 15200874; PubMed Central PMCID: PMC3323099.
4. **Dumler JS, Taylor JP, Walker DH.** Clinical and laboratory features of murine typhus in south Texas, 1980 through 1987. *JAMA.* 1991 Sep 11;266(10):1365-70. PubMed PMID: 1880866.
5. **Whelton A, Donadio JV Jr, Elisberg BL.** Acute renal failure complicating rickettsial infections in glucose-6-phosphate dehydrogenase-deficient individuals. *Ann Intern Med.* 1968 Aug;69(2):323-8. PubMed PMID: 5695625.
6. **Lee N, Ip M, Wong B, Lui G, Tsang OT, Lai JY, Choi KW, Lam R, Ng TK, Ho J, Chan YY, Cockram CS, Lai ST.** Risk factors associated with life-threatening rickettsial infections. *Am J Trop Med Hyg.* 2008 Jun;78(6):973-8. PubMed PMID: 18541779.
7. **Walker DH, Parks FM, Betz TG, Taylor JP, Muehlberger JW.** Histopathology and immunohistologic demonstration of the distribution of *Rickettsia typhi* in fatal murine typhus. *Am J Clin Pathol.* 1989 Jun;91(6):720-4. PubMed PMID: 2499181.
8. **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.

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