CLINICAL VIGNETTE

Suspected Murine Typhus in a Young, Unhoused Man

Emily Martey, BA and Christine Dang, MD

Case

A 25-year-old previously healthy, unhoused male with no significant past medical history presented to the emergency department with one week of severe headache, back pain, and fever up to 39.2°C. Review of systems was also positive for nausea and myalgias. He denied photophobia, neck stiffness/ pain, vomiting, cough, shortness of breath, palpitations, abdominal pain, diarrhea, dysuria, or recent spinal trauma.

The patient's social history was notable for living in a makeshift shelter by the freeway, with rats and stray cats in the surrounding area. Multiple people lived in the encampment, including one who was recently hospitalized due to "spider bites." The patient smoked one-half pack of cigarettes per day and denied current or prior intravenous drug use. He was sexually active with consistent condom use within the past six months and denied any history of sexually transmitted infection.

Initial vital signs were notable for HR 130 and T 39.2°C. On physical examination, he had mild conjunctival injection, but no skin rash. There was no nuchal rigidity, with mild cervical lymphadenopathy. Heart rate was tachycardic with regular rhythm and no murmur. Lungs were clear to auscultation bilaterally. The abdomen was soft and non-tender. He had tenderness in the right lower back without spinal tenderness.

Initial laboratory results included leukocytosis of 11,600 cells/$mm^{3.}$ platelet count of 145,000 cells/mm^3. Sodium 128 mmol/L, albumin 3.3 g/dL, alkaline phosphatase 239 U/L, alanine aminotransferase (ALT) 355 U/L, aspartate aminotransferase (AST) 168 U/L, C-reactive protein (CRP) 130.4 mg/L, lactate dehydrogenase (LDH) 457 U/L, and lactate 2.2 mmol/L. Urinalysis was significant for microscopic hematuria (11 to 25 RBC/HPF). Urine toxicology screen was positive for amphetamines and opiates. SARS-CoV-2 (COVID-19), Influenza A and B, and RSV PCR tests were negative. Blood, MRSA nares, and urine cultures were collected.

CT chest, abdomen and pelvis with contrast showed a 2.1 cm right middle lobe consolidation with surrounding ground glass appearance, with borderline enlargement of liver and spleen. On right upper quadrant ultrasound, the liver and spleen were normal in size, with a homogenous 6 mm echogenic lesion consistent with a gallbladder polyp. Chest x-ray showed only mild, irregular bibasilar opacities. Follow-up CT thorax without contrast confirmed the presence of a right middle lobe focal consolidation. MRI of the lumbar spine showed no evidence of an epidural abscess or discitis/osteomyelitis. CT head without contrast was non-suggestive of intracranial hemorrhage or meningitis.

Given the presence of fever, transaminitis, leukocytosis, thrombocytopenia, and imaging concerning for a pulmonary consolidation in the context of significant rat exposure, the differential diagnosis included community-acquired pneumonia (including Legionella), HIV, and zoonotic diseases such as Q fever, leptospirosis, and murine typhus. Fungal infections such as coccidioidomycosis, were also considered. The patient was started on IV ceftriaxone and oral azithromycin to cover for community-acquired pneumonia (CAP), and also started on oral doxycycline for suspected typhus given lab abnormalities and social and environmental risk factors.

An infectious etiology was strongly suspected due to the presence of sepsis with 2/4 SIRS criteria and leukocytosis with an elevated CRP on admission. Initial infectious evaluation included HIV antigen/antibody, an acute hepatitis panel (heaptitis A total antibody, hepatitis C antibody, hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody), coccidioidomycosis IgM/IgG antibodies, syphilis, and cryptococcus antigen. Infectious Diseases was consulted on hospital day 2. At that time, a diffuse macular rash had developed on the abdomen and extremities, with sparing of the palms and soles. Further infectious testing based on cat/rat exposure included rickettsial serology, *Bartonella* serology, *Coxiella burnetii* DNA, Q Fever serology, HIV antibody/ antigen, *Leptospira* DNA, QuantiFERON-TB Gold, and urine chlamydia/gonorrhea. Azithromycin and ceftriaxone were stopped, as symptoms and imaging studies were less consistent with CAP. Doxycycline was continued throughout the hospital course with resolution of fever on hospital day 3.

Infectious testing results included a positive hepatitis C antibody with undetectable Hepatitis C viral load. Hepatitis A antibodies, hepatitis B surface antigen/antibody, HIV antigen/ antibody, syphilis, coccidioidomycosis antibodies, cryptococcus antigen, Q Fever PCR, TB, *Bartonella* serology, *C. burnetii* serum DNA, *Leptospira* urine DNA, *Legionella* urine antigen, and urine chlamydia and gonorrhea were all negative. Blood, urine, and MRSA cultures were also negative.

West Nile Virus (WNV) serology was pending at the time of discharge. Lumbar puncture was not obtained due to improvement of headache symptoms and defervescence on doxycycline. *R. typhi* IgM antibody was positive with a titer of 1:64 and *R. typhi* IgG antibody was negative. Given the full resolution of symptoms by hospital day #4, the patient was discharged with a recommendation to complete a fourteen-day course of doxycycline and to follow up with a primary medical provider within one to two weeks after discharge. Convalescent titers to confirm murine typhus were not obtained four to six weeks after discharge, as planned, because the patient did not return for his follow up appointment.

Discussion

Murine typhus, or "endemic typhus", is a flea-borne, febrile illness caused by *Rickettsia typhus,* an obligate intracellular, gram-negative bacterium that belongs to the typhus group *Rickettsia*.[1] Another member of the typhus group includes *R. prowazekii*, the causative agent of epidemic typhus.[2] Unlike epidemic typhus, which is spread from person to person and is associated with a higher mortality rate, murine typhus is spread by fleas that become infected upon feeding on animals that carry *R. typhus*, such as rats, cats, opossums, and even pet dogs and cats that frequently go outside.[2,3] The infected fleas transmit disease to humans through flea bites and exposure to feces via broken skin, inhalation, or mucosal contact. Cases of murine typhus have been reported worldwide, with a higher prevalence in subtropical and tropical regions.[1,2,4,5] In the United States, the geographic distribution of murine typhus is concentrated in Southern California, Southern Texas, and Hawaii.[3] In California, murine typhus is endemic in Orange County and Los Angeles County, which has the highest incidence of cases in the state.[6] The disease occurs year-round, with more cases reported during the warmer months.[7] Over the last decade, Los Angeles County cases increased to a total of 176 in 2021, surpassing the 149 cases reported by the Department of Public Health in 2018.[6]

Clinical manifestations of murine typhus include fever, chills, headache, and myalgia.[3] A maculopapular or petechial rash can appear within one week of symptom onset. The rash typically originates on the trunk and subsequently spreads to the extremities with sparing of the palms and soles.[1] The classic triad of fever, rash, and headache is only reported in one-third of cases, and rash is reported in less than half of cases.[1] Common laboratory findings include mildly elevated liver transaminases, elevated LDH, a high erythrocyte sedimentation rate (ESR), hypoalbuminemia, thrombocytopenia, and hyponatremia.[1]

Murine typhus typically presents with mild illness, but if left untreated, can result in severe disease with renal, cardiac, pulmonary, hepatic, or neurologic involvement.[1,8,9] Mortality of patients who do not receive antibiotic therapy is estimated to be 4%.[2,5] A high index of suspicion is necessary for prompt diagnosis given murine typhus is a rare disease in the United States with a non-specific clinical presentation.[10]

For the diagnosis of murine typhus, serologic testing for IgM and IgG serum antibodies is necessary. IgM antibodies are inferior to IgG antibodies due to inconsistent sensitivity in the acute phase of infection.[11] A single positive titer is inadequate to confirm the diagnosis of murine typhus, and a four-fold increase between acute and convalescent IgG titers is recommended for diagnosis.[12] First-line treatment for murine typhus is doxycycline.[10] Recommended duration of treatment is a minimum of five days or at least 48 hours after defervescence.[12] For patients with contraindications to doxycycline, azithromycin is the recommended second-line treatment, and chloramphenicol is a third-line option.[13] It is essential to treat all suspected patients with typhus immediately, even if confirmatory testing is not available.

People who are unhoused and live in environmental conditions that further the growth of rodents and other animals likely to carry infected fleas are particularly vulnerable to vector-borne diseases like typhus. This population is also at higher risk of acquiring infections with fecal-oral transmission, such as Hepatitis A. The unhoused crisis, which has only been exacerbated by the COVID-19 pandemic in Los Angeles and across the United States, is a major public health concern given the risk posed by the rise of communicable diseases in densely populated urban centers. With increasing incidence of murine typhus, particularly among unhoused people and other individuals with significant exposure to flea-infected animals, it is imperative for clinicians to consider this disease in patients who present with undifferentiated febrile illness and relevant exposure history. Murine typhus is often misdiagnosed and underreported given most cases are mild and associated with non-specific, self-limiting symptoms such as fever, myalgia, and headache which mimic viral infections, including COVID-19.[2,14] Clinical presentation, common laboratory abnormalities, and a thorough social history should be used collectively to identify and treat murine typhus.

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