CLINICAL VIGNETTE

Avoid Those Flea Bites: A Local Case of Murine Typhus

Eric J. Kwoh, MD and Jonathan M. Helali, MD

Case Report

A 38-year-old male with a past medical history of generalized anxiety disorder presented to the emergency department with 2 weeks of subjective fever, myalgias, headaches, photophobia, nausea, and diarrhea. He denied any recent travel or sick contacts. He did report recent unprotected sex with a new female partner he met on a mobile dating app. He lives alone in an apartment with a pet dog and turtle and hikes several times a week. His initial vitals were normal except for a temperature of 101.2ºF. On physical exam, he appeared uncomfortable with mild nuchal rigidity. Laboratory studies revealed a mild thrombocytopenia (121 k/uL) and a mild hyponatremia (132 mmol/L). A chest radiograph was unremarkable. Given the plausible concerns for meningitis, a lumbar puncture was performed which demonstrated normal cerebrospinal fluid findings. Patient was presumed to have a viral illness and discharged home.

He returned to the emergency department 3 days later with persistent fevers, worsening headache, myalgias, nausea, and diarrhea. He also reported atypical chest pain which he attributed to anxiety. Vitals were significant for a temperature of 103.1ºF, heart rate 104 beats/min, blood pressure 133/79 mmHg, respiratory rate 26 breaths/min, and oxygen saturation of 96% on room air. Physical exam was significant for mild abdominal tenderness in the right upper and lower quadrants without guarding or rebound, and rest of his physical exam was unremarkable. Laboratory studies revealed a mild leukopenia with 84% neutrophils and 7% bands, a worsening thrombocytopenia to 62 k/uL as well as a worsening hyponatremia to 128 mmol/L. Other laboratory abnormalities included a mild transaminase elevation, AST 98 U/L and ALT 78 U/L, an elevated procalcitonin to 2.58 ng/mL, and elevated C-reactive protein to 10.8 mg/dL. Troponin levels and EKG were both unremarkable. Blood cultures were obtained. Computed tomography imaging of the chest/abdomen/pelvis revealed a focal airspace opacity in the anterior left upper lobe, a left 1 cm supraclavicular node, and hepatosplenomegaly. Covid-19 and influenza PCR testing were both negative.

The patient met sepsis criteria with presumed diagnosis of community-acquired pneumonia (CAP) based on imaging, and was admitted for further workup and management. However, patient did not report any clinical symptoms of pneumonia and his overall presentation was not typical for CAP. A broad differential diagnosis was considered, these include an alternative occult bacterial infection, supported by elevated procalcitonin and bandemia, acute HIV, with recent unprotected sex with new partner, salmonella and rickettsial illness given hiking history and pet dog and turtle. Malignancy was considered with hepatosplenomegaly and worsening thrombocytopenia/ leukopenia. Infectious Diseases consult was obtained and a broad infectious testing was sent including blood cultures, HIV, Hepatitis panel, Histoplasma serologies, Coccidioidomycosis serologies, Brucella serologies, Bartonella serologies, Q fever serologies, Rickettsia typhi serologies, Salmonella serologies, RPR, Quantiferon gold, Legionella urine antigen, respiratory pathogen panel, peripheral smear, stool culture and PCR, and Clostridium difficile PCR. Patient was started on empiric ceftriaxone and doxycycline for occult bacterial infection, community-acquired pneumonia, and rickettsial diseases. On hospital day 2, patient developed a mild anemia with worsening thrombocytopenia to 42 k/uL and continued mild leukopenia. Hematology/Oncology consult recommended consideration of bone marrow biopsy if infectious workup was negative.

On hospital day 3, the patient defervesced, however, he developed transient word-finding difficulty and slightly decreased visual acuity. MRI brain was unremarkable. The following day, the patient was feeling back to baseline with complete resolution of his fever, headaches, diarrhea and myalgias. His visual acuity also returned to normal with no further episodes of word-finding difficulty.

On hospital day 5, serologies (IgM and IgG) for Rickettsia typhi returned positive. The remainder of his infectious testing was negative. His pancytopenia, hyponatremia, and transaminitis improved and he was discharged on oral doxycycline 100 mg twice daily to complete a 10-day course with infectious disease follow-up.

Discussion

Murine typhus is often referred to as “flea-borne typhus” and is caused by *Rickettsia typhi*, a Gram-negative, obligately intracellular bacteria. It is transmitted to humans primarily by the rat flea *Xenopsylla cheopis*—and rats are the common reservoir, with opossums and domestic cats also reservoirs in suburban areas.[1,2] Infection occurs when humans inoculate the infective flea feces into bite wounds in the skin. Murine typhus has a worldwide distribution with the majority of outbreaks occurring in Southeast Asia, North Africa, and North America. Murine typhus was first described in the United States in 1913,

and reached a peak of over 5000 cases in 1944.[3] The incidence of murine typhus declined significantly after initiation of DDT to control rat fleas, use of complement fixation lab confirmation of suspected cases, and the widespread use of antibiotics for treatment.[3] Now, while murine typhus is considered endemic in Los Angeles and Orange County, Texas, and Hawaii, there are about 300 confirmed cases reported each year in the United States. [4] The actual incidence is almost certainly higher as murine typhus is not reported by all state health departments, and underdiagnosed as it is easily mistaken for a viral illness. Since symptoms are often mild and self-limiting, and patients are rarely aware of having flea bites.[5] In 2019, there were 77 confirmed cases of murine typhus reported in California.[4]

Clinical manifestations of murine typhus generally follow an incubation period of 6 to 14 days, after which an abrupt onset of high fever, headache, myalgias, weakness, and a centrally distributed maculopapular rash.[6] The rash of murine typhus, if present, typically begins in the trunks and spreads peripherally, sparing palms and soles.[2] The classical triad of fever, headache, and rash only occurs in 35-49% of patients.[7] In one review of 137 patients, fever was present in 100% of subjects and rash was present in 20%.[8] Nonspecific gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea may also occur. Given the nonspecific nature of these clinical signs and symptoms, it is often difficult to establish or narrow the diagnosis on clinical presentation alone. Most patients will experience mild self-limiting symptoms, but more severe disease can occur especially if left untreated. Patients with severe disease can develop a wide spectrum of illness including acute kidney injury from decreased renal perfusion and acute interstitial nephritis, cough and dyspnea from interstitial infiltrates, relative bradycardia, splenomegaly (15-20% of patients), hepatomegaly, mental confusion with focal neurologic symptoms, meningitis, uveitis, and septic shock with multiorgan failure.[5,8,9] Our patient's abnormal pulmonary imaging, acute transient neurologic symptoms, hepatosplenomegaly, and initial sepsis criteria reflected severe presentation.

Laboratory abnormalities for murine typhus include thrombocytopenia reported in 48% of patients.[9] Hyponatremia, elevated creatine kinase levels, and abnormal liver tests are frequently present. Mild leukocytosis or leukopenia may occur, but the white blood cell count is usually normal.[9] This patient presented with thrombocytopenia, hyponatremia, mild transaminitis, and mild leukopenia.

An indirect immunofluorescence antibody assay is the preferred serologic test since it provides quantitative results. This method of testing requires two samples collected weeks apart—generally an acute specimen is collected in the first two weeks of illness and a convalescent specimen is collected two to four weeks later. Confirmation requires a fourfold rise in IgG antibody titers. Additionally, *R. typhi* antigens can cross-react with other Rickettsia groups, *R. prowazekii* from the typhus group, *R. rickettsia* from the spotted fever group and cannot provide species-specific results.[10] IgM assays for *R. typhi* can be used in acute illness with reasonable specificity but have variable sensitivity. Thus absence of detectable IgM does not rule out acute disease.[5] Only 15-55% of patients have reactive antibodies within the first week of illness.[8] This demonstrated positive IgM and IgG assays for *R. typhi* two weeks after onset of symptoms, with the positive IgM results establishing the firm diagnosis in the context of the patient's clinical presentation.

Empiric treatment is recommended for all patients with suspected murine typhus. Adults account for the majority of those infected, but children have represented 75% of infections in some outbreaks.[11] Doxycycline is the preferred agent for treatment of murine typhus with a usual treatment duration of 7-10 days. A prospective randomized trial showed greater efficacy with doxycycline compared to azithromycin with decreased duration of fever and lower progression to severe disease in those treated with doxycycline.[12] In an observational study involving 137 patients, 79% of those who received doxycycline were afebrile within 48 hours compared to 15% in the untreated group, and only two patients died.[8] The case fatality rate of murine typhus remains low and was reported to be 0.3% in a review of 1,801 patients reported.[7]

Conclusion

Murine typhus remains vastly underdiagnosed and underreported, even in endemic regions such as Los Angeles. This continues to be a challenging diagnosis given its nonspecific clinical signs and symptoms, and a high index of suspicion is needed to establish the diagnosis. A relatively undifferentiated febrile illness in a patient with rash, headache, and thrombocytopenia should raise suspicion for murine typhus. Clinical history should be closely reviewed for any exposure to pets, wild animals, or flea bites. Empiric treatment should be started in all patients where murine typhus is suspected because failure to treat can lead to more severe multi-system disease requiring hospitalization such as in our patient. Serologic testing can help establish the diagnosis, but results are often negative during acute infection which makes early clinical recognition and empiric therapy imperative. Treatment of murine typhus with doxycycline is highly effective and any fevers that persist despite adequate therapy should raise the suspicion for an alternative diagnosis.

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