




Ischemic Hepatitis and Septic Shock Secondary to Murine Typhus Infection in Pregnancy

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Abstract

Infection with murine typhus may be associated with significant morbidity. With nonspecific symptoms and laboratory abnormalities, diagnosis may be challenging. In this case, a pregnant patient presented with complaints of fevers and myalgias. Her laboratory results included severe transaminitis as well as thrombocytopenia and hyponatremia. She ultimately required vasopressor support and intensive care unit admission despite fluid resuscitation and broad-spectrum antibiotics. Empiric doxycycline was initiated due to suspicion for murine typhus, which laboratory testing later confirmed. Her clinical status improved with these interventions. This was a severe case of murine typhus resulting in septic shock and ischemic hepatitis. It is important to know the typical findings of murine typhus and consider it in a differential diagnosis, especially when practicing in endemic areas.

Keywords

- ▶ murine typhus
- ▶ ischemic hepatitis
- ▶ septic shock

Murine typhus is a flea-borne infection that is caused by the bacterium *Rickettsia typhi*. It is endemic to some areas in the United States, with clusters of cases reported in California, Texas, and Hawaii. Outbreaks have mostly been associated with close contact with flea-bearing hosts (most commonly cats, rodents, and opossums), which then transmit the disease to humans. Symptoms are usually nonspecific including fever, myalgias, headache, and petechial rash. Laboratory abnormalities are generally nonspecific but characteristically include thrombocytopenia, abnormal liver function tests, hyponatremia, hypoalbuminuria, and cerebrospinal fluid studies consistent with aseptic meningitis. Although most cases are mild and self-limited, if left untreated, the disease can progress to severe neurologic, hepatic, cardiac, renal, and/or pulmonary dysfunction.¹

Case

A 37-year-old G9P6026 woman presented to an obstetrical triage unit in Galveston, Texas, at 32 weeks and 6 days of gestation complaining of fevers and myalgias for the past 7 days. Vital signs were significant for tachycardia, hypotension, and fever. Additionally, a papular rash was noted on her abdomen, extending to her lower extremities bilaterally. Laboratory results were significant for transaminitis with alanine aminotransferase (ALT) of 1,485 U/L and aspartate aminotransferase (AST) of 1,367 U/L, thrombocytopenia (platelet [plt] = $83 \times 10^3/\mu\text{L}$), hyponatremia (Na = 128 mmol/L), lactic acidosis (lactic acid = 3.21 mmol/L), bandemia (white blood cells [WBC] = $5.77 \times 10^3/\mu\text{L}$ with markedly increased bands), and hyperbilirubinemia (total bilirubin = 4.2 mg/dL,

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conjugated = 2.2 mg/dL). A bedside transthoracic echocardiogram revealed normal biventricular function, a hyperdynamic left ventricle, a collapsing inferior vena cava with inspiration, and no evidence of pulmonary edema. Fluid resuscitation and broad-spectrum antibiotics with piperacillin/tazobactam, as well as acyclovir, were initiated.

On hospital day 2, she was noted to have persistent hypotension with mean arterial pressure (MAP) of 50 mm Hg, tachycardia, and tachypnea. She required 2 L/min of oxygen via nasal cannula to maintain oxygen saturations above 94% and developed acute kidney injury. Norepinephrine was started through a peripheral intravenous line to maintain MAP above 65 mm Hg. Antibiotic coverage was broadened to include doxycycline due to clinical suspicion of murine typhus as while initial resuscitation and empiric broad-spectrum antibiotics improved the liver function tests and hemodynamic parameters, the patient remained febrile.

Over the following week, cultures and hepatitis workup were negative. Lumbar puncture indicated aseptic meningitis. On hospital day 4, *R. typhi* immunoglobulin M (IgM) antibodies returned positive to confirm the diagnosis of murine typhus. She was discharged on hospital day 6 after gradual improvement of her transaminitis. The remainder of her pregnancy was complicated by the development of preeclampsia with severe features at 36 weeks of gestation based on mild-ranging blood pressures and persistent neurologic symptoms. She underwent induction of labor and had an uncomplicated spontaneous vaginal delivery.

Discussion

Murine typhus is caused by infection with the bacterium *R. typhi*. Fleas serve as a vector for the bacterium, and the classic transmission pattern occurs between fleas and small mammals. Transmission to humans occurs when there is contact with an infected flea and *R. typhi* enters the human bloodstream. Once transmission occurs, the incubation period is approximately 1 to 2 weeks. The presentation is generally nonspecific and without antimicrobial treatment, the time to defervescence ranges from 12 to 21 days. While murine typhus infections are generally self-limiting, they have the potential to cause significant morbidity.

This was a severe case of murine typhus resulting in septic shock and ischemic hepatitis. Ischemic hepatitis is the result of sustained hypotension/hypoperfusion and may be associated with significant morbidity and mortality. In one meta-analysis, ischemic hepatitis was present in 2.5% of intensive care unit admissions, and there was an associated in-hospital mortality rate among these patients of approximately 50%.² Ischemic hepatitis is characterized by a significant increase in serum transaminases, with levels reaching up to 25 to 250 times the upper limit of normal.³ Common etiologies include left and right ventricular failure, hemorrhagic shock, and sepsis-induced hypotension. Aggressive hemodynamic resuscitation and treatment of the underlying cause usually results in complete recovery; however, on rare occasions,

progression to acute liver failure may ensue.⁴ Following timely resuscitation, serum aminotransferase levels return to normal within 7 to 10 days.³

In this case, the underlying disease process inciting ischemic hepatitis was septic shock secondary to murine typhus. In patients with septic shock, fluid administration is vital in management to maintain tissue perfusion. In this patient, the ischemic hepatitis was ultimately resolved with supportive care and fluid administration.

Early diagnosis and treatment of murine typhus is important to prevent the development of severe complications. While laboratory confirmation of the diagnosis of murine typhus infection may take up to several days, it is important to hold a level of suspicion when patients present with its classic findings, particularly in endemic areas.

Doxycycline is the treatment of choice for murine typhus, and empiric initiation is recommended if the infection is suspected. Once doxycycline is initiated, a rapid clinical response is generally appreciated, with mean time to defervescence being 35 hours.⁵ Doxycycline has traditionally been avoided in pregnancy due to the association of tetracyclines with effects on fetal bones and teeth. These adverse effects have been primarily seen with older tetracyclines, and have not been associated with doxycycline use.⁶ Azithromycin has been suggested as an alternative to doxycycline in the treatment of murine typhus; however, there are data demonstrating inferior efficacy.⁵ Additionally, azithromycin has been associated with hepatotoxicity due to its hepatic clearance and should be used with caution in those with hepatic dysfunction.⁷

Outside of an infectious process, the differential diagnosis for this patient included pregnancy-specific complications of HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome and acute fatty liver of pregnancy. There are many overlapping common laboratory abnormalities between these conditions and murine typhus including transaminitis, thrombocytopenia, and conjugated bilirubinemia. What may aid to differentiate murine typhus from HELLP syndrome and acute fatty liver of pregnancy is the evidence of an infectious process, rash, and hyponatremia. It is important to distinguish from these pregnancy-specific conditions to avoid unnecessary preterm delivery and perinatal morbidity.

Murine typhus should be suspected in endemic areas in patients presenting with febrile illness accompanied by thrombocytopenia, rash, hyponatremia, and transaminitis. Treatment with doxycycline should be considered during pregnancy to avoid serious complications including development of septic shock.

Note

Each author has confirmed compliance with the journal's requirements for authorship.

Conflict of Interest

None declared.

References

- 1 Tsioutis C, Zafeiri M, Avramopoulos A, Prousalis E, Miligkos M, Karageorgos SA. Clinical and laboratory characteristics, epidemiology, and outcomes of murine typhus: a systematic review. *Acta Trop* 2017;166:16–24
- 2 Tapper EB, Sengupta N, Bonder A. The incidence and outcomes of ischemic hepatitis: a systematic review with meta-analysis. *Am J Med* 2015;128(12):1314–1321
- 3 Lightsey JM, Rockey DC. Current concepts in ischemic hepatitis. *Curr Opin Gastroenterol* 2017;33(03):158–163
- 4 Taylor RM, Tujios S, Jinjuvadia K, et al. Short and long-term outcomes in patients with acute liver failure due to ischemic hepatitis. *Dig Dis Sci* 2012;57(03):777–785
- 5 Newton PN, Keolouangkhot V, Lee SJ, et al. A prospective, open-label, randomized trial of doxycycline versus azithromycin for the treatment of uncomplicated murine typhus. *Clin Infect Dis* 2019;68(05):738–747
- 6 Cross R, Ling C, Day NP, McGready R, Paris DH. Revisiting doxycycline in pregnancy and early childhood: time to rebuild its reputation? *Expert Opin Drug Saf* 2016;15(03):367–382
- 7 Martinez MA, Vuppalanchi R, Fontana RJ, et al. Clinical and histologic features of azithromycin-induced liver injury. *Clin Gastroenterol Hepatol* 2015;13(02):369–376.e3