CLINICAL VIGNETTE

Murine Typhus Mistaken for Strep Throat

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Clinical Case

A 74-year-old man presented to the ER complaining of sore throat and pleuritic chest pain. He describes the chest pain which started the day prior as associated with breathing, intermittent, non-radiating and non-exertional. He also reported onset of fevers to 101.9 degrees F and chills the day prior, as well as sore throat and headache. He denies shortness of breath, nausea, vomiting, abdominal pain, dysuria or changes in bowel habits. He recently traveled to Seattle and visited his grandchild who was sick. Acute Coronary Syndrome was ruled out with negative EKGs and troponins. Chest x-ray was unremarkable. Swabs for influenza A/B, COVID and RSV were all negative. A rapid strep test was positive, and he was started on amoxicillin 500 mg PO BID and discharged home. Over the next few days at home, he continued to have fevers and chills with maximum temperature of 102.6 degrees F and returned to clinic 3 days later. He was switched from amoxicillin to cefdinir 300 mg PO BID. Blood cultures were collected and returned negative. Transthoracic echocardiogram showed normal LVEF and no vegetations. Chest x-ray showed new left perihilar consolidation and azithromycin and cefdinir were started. He continued to have fevers to 102 degrees F at home and returned to the ER. He reported worsened pleuritic chest pain over two days along with a nonproductive cough with worsening fatigue and malaise. He denied orthopnea, shortness of breath, leg swelling, nausea, abdominal pain, urinary symptoms, rashes or changes in bowels. His past medical history includes paroxysmmal atrial fibrillation, gastroesophageal reflux disease, hyperlipidemia and prostatectomy for prostate cancer. Medications include Apixaban 5 mg BID and Rosuvastatin 10 mg daily. Family history is unremarkable. He is married and lives with his wife and has no pets. He works at the museum, enjoys hiking and never smoked or used recreational drugs. Alcohol is an occasional glass of wine. He enjoys collecting rocks from roadsides around Topanga Canyon and brings them to his backyard. He has noticed rhinorrhea for the past 3 weeks after he comes back from these trips. He also traps and relocates raccoons and gophers. He denies recent flea or tick bites but reports frequent chigger bites. The patient was admitted to the hospital for persistent fever of unknown origin.

His admission exam included slightly low blood pressure at 96/67, pulse at 65, temperature 100.7 degrees F and room air oxygen saturation of 98%. Pertinent exam findings included no distress, normal sclerae and conjunctivae and pupils with intact extraocular movements. Mucus membranes were moist, with normal tympanic membranes, clear oropharynx, and no cervical lymphadenopathy or neck masses. Chest had faint bilateral crackles, CV had regular rate and rhythm, no murmurs and symmetric distal pulses. His abdomen was soft, non-tender without masses and cranial nerves II-XII were intact. Strength and sensation were symmetrically intact.

Laboratory evaluation revealed normal WBC and platelet counts with slightly low hemoglobin of 11.5. Electrolytes and creatine/BUN were normal. Transaminases were abnormal with elevated alkaline phosphatase at 466, AST 124 and ALT 131 and low albumin of 2.9. Total bilirubin was normal at 0.4. Infectious Diseases was consulted and patient was started on piperacillin/tazobactam and Ceftriaxone for broad-spectrum antibacterial coverage. Serologies for Cocci, Aspergillus, Cryptococcus, Epstein Barr virus, CMV, HIV, COVID, Legionella, influenza, Strep antigen, acute hepatitis panel and Francisella tularensis were all negative. Rickettsia IgM also returned negative. CT Chest showed large left suprahilar mass with adjacent groundglass and bilateral pulmonary micronodules. Abdominal ultrasound showed normal gall bladder and mild hepatomegaly. Repeat transthoracic echocardiogram showed normal LVEF and no vegetations. Based on the history and potential environmental exposures, Infectious Diseases highly suspected murine typhus and recommended a 14-day course of oral doxycycline. The patient's fevers resolved and he clinically improved back to his baseline. Repeat outpatient CT Chest confirmed interval resolution of his lung infiltrates.

Discussion

Murine typhus is a flea-borne infectious disease caused by Rickettsia typhi, an obligate intracellular, gram-negative bacteria. Murine typhus is most often transmitted by the rat flea, Xenopsylla cheopis. Once infected with R. typhi, the flea hosts are permanently infected although their lifespan is not impacted. Humans are infected by inoculation of infective flea feces into broken skin. Murine typhus has a worldwide distribution, with the majority of infections occurring in Southeast Asia, North Africa, the Mediterranean region and North America. The majority of cases of murine typhus occur in areas with large numbers of rats, however, in suburban locations in the United States, domestic cats and opossums are common sources for flea hosts.[1-3]

Murine typhus is found in different environments ranging from hot to cold, humid to semi-arid. Although murine typhus can be

found year-round, infections tend to increase during hot, dry periods such as late summer and early fall.[3,4] Interestingly, murine typhus is not reported in surveillance data by most state health departments so it may be more prevalent than we realize. It is certainly underdiagnosed, as it is easily mistaken for a viral illness, and many cases resolve spontaneously. One study from Texas reported 13 percent of children aged 1 to 17 years had IgG antibodies reactive to R. typhi consistent with underdiagnosed infections.[5] The primary pathophysiology of R. typhi infection is an inflammatory vasculitis characterized by perivascular infiltration of lymphocytes, macrophages, plasma and mast cells.[6]

Murine typhus has an incubation period from 8 to 16 days. The onset of symptoms is usually abrupt with nonspecific symptoms including rash and fever. The classic clinical triad of fever, headache and rash only occurs in 35 to 49 percent of patients. The most prominent early symptoms are fever, chills, headache and myalgias. Other less common early symptoms are nausea, vomiting, abdominal pain and diarrhea. The rash is most commonly a maculopapular eruption on the trunk which then spreads peripherally, sparing the palms and soles. It usually occurs at the end of the first week of illness. The reported frequency of this rash ranges from 20 percent to 54 percent. The vast majority of patients with murine typhus experience mild symptoms, however severe disease is possible and can present with neurologic, hepatic, cardiac, renal and/or pulmonary dysfunction. Renal dysfunction can occur due to decreased renal perfusion and acute interstitial nephritis. Microscopic hematuria and proteinuria is reported in up to one-third of patients. Pulmonary dysfunction can include interstitial infiltrates on chest radiographs or pulmonary edema. Ocular manifestations include exudates, hemorrhage or vitreal inflammation due to widespread vasculitis. Myocarditis is rarely reported and splenomegaly detected in 15 to 20 percent of patients. Risk factors for progressing to severe or fatal disease include advanced age and G6PD deficiency. Laboratory findings in murine typhus are usually nonspecific including thrombocytopenia, mild leukocytosis or leukopenia, hyponatremia, hypoalbuminuria, elevated creatine kinase levels and abnormal liver function tests (as in our patient).[7,8]

Diagnosis of murine typhus can be challenging. There is no reliable diagnostic laboratory test in the early phase of the illness. The initial diagnosis and decision to treat is based on clinical and laboratory findings in a patient with potential exposure to fleas or flea-bearing hosts. However, many patients are unaware of flea bites. In patients with suspected murine typhus infection, the diagnosis can be confirmed serologically with an indirect fluorescent antibody test after a course of empiric therapy. The diagnosis of murine typhus is confirmed by a fourfold antibody rise in IgG titer between acute and convalescent serum samples, usually taken at least two weeks apart. IgM assays for murine typhus are not sensitive. Absence of detectable IgM should not be used to rule out acute murine typhus infection. Polymerase chain reaction (PCR)-based tests can also be used to confirm the diagnosis of murine typhus, however these tests are not widely available and can have poor sensitivity due to low levels of rickettsemia that vary by stage of illness. The differential diagnosis for murine typhus is broad given its nonspecific symptoms at presentation and can include viral, spirochetal, rickettsial and other bacterial infections as well as non-infectious etiologies such as drug reactions or Kawasaki disease.[7,8]

Guidelines recommend empiric treatment for all patients with a suspected diagnosis of murine typhus. Although spontaneous recovery generally occurs within two weeks in untreated patients, antibiotics significantly shorten the duration of illness and help prevent rare fatalities. In a systematic review on 1135 patients, time to defervescence was 1.5 to 4 days for patients who received antibiotic treatment, versus 12 to 21 days in untreated patients.[3] Another study of 213 children in Texas reported the mean duration of hospitalization was shorter at 2.7 days for treated patients versus 4.1 days for untreated patients.[8] The preferred agent for treatment of murine typhus is doxycycline until at least 48 hours after defervescence or for seven days, whichever is longer. If there is an absolute contraindication to doxycycline, then other agents can be used such as azithromycin, chloramphenicol or ciprofloxacin. However, these other agents are less effective.[9]

Conclusion

Murine typhus is underdiagnosed and easily mistaken for a viral illness. Our patient presented with symptoms consistent with an upper respiratory infection which was diagnosed as strep throat on initial presentation. However, his fevers persisted despite several courses of antibiotics. With careful history taking, a diagnosis of murine typhus infection was made and the patient was switched to doxycycline, the appropriate antibiotic and made a full recovery.

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