



> THE PATIENT

72-year-old man

> SIGNS & SYMPTOMS

- Fever
- New-onset urinary frequency
- Altered mental state

CASE REPORT

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> THE CASE

A 72-year-old man was admitted to our Dallas hospital with a 4-day history of fevers and new-onset urinary frequency. He did not report any joint pain, sick contacts, or recent travel or recall any skin findings (rashes, insect bites). Past medical history was significant for hypertension, hyperlipidemia, diabetes, benign prostatic hyperplasia, recurrent urinary tract infections, and lumbar radiculopathy.

Initial signs and symptoms were suggestive of sepsis: a temperature of 102.7 °F, tachycardia, and a suspected genitourinary infection. This was supported by initial labs concerning for end-organ damage: elevated creatinine of 1.58 mg/dL (reference range, 0.67-1.17 mg/dL), elevated international normalized ratio (INR) of 1.6 (reference range, 0.9-1.1), hemoglobin of 12.8 g/dL (reference range, 13.5 - 17.5 g/dL), and platelet count of $99 \times 10^9/L$ (reference range, $160-383 \times 10^9/L$).

Over the next several days, the patient's condition worsened, and he experienced a decline in mental status, despite initiation of broad-spectrum antibiotics and fluid resuscitation. Although lumbar puncture was warranted, neither Neurology nor Interventional Radiology were willing to risk the procedure given the patient's worsening hemoglobin (8.3 g/dL) and platelet count ($51 \times 10^9/L$).

Preliminary work-up included a urinalysis negative for leukocytes, nitrites, and bacteria—despite a urine culture that showed gram-positive cocci. His chest x-ray was unremarkable, and computed tomography of his brain showed generalized atrophy without acute changes. The work-up was expanded to fungal cultures and immunochemical assays. Empiric treatment with micafungin and acyclovir was started without improvement.

■ **Further conversation with family revealed** that the patient liked to spend time outdoors and he'd had a similar episode in which he'd been diagnosed with an unknown disease from an insect bite. Pertinent negative tests included: HIV, syphilis, rapid heterophile antibody, influenza, respiratory virus panel, blood culture, fungal culture, antineutrophil cytoplasmic antibodies, histoplasmosis, brucellosis, malaria, Epstein-Barr virus, cytomegalovirus, and parvovirus. *Coxiella burnetii* and West Nile virus immunoglobulin (Ig) G were positive, suggesting a prior exposure.

THE DIAGNOSIS

Given these new findings and reported outdoor activities, Infectious Diseases recommended we start our patient on doxycycline for possible rickettsia infection. On Day 8, doxycycline 200 mg IV once daily was started. (The IV form was initiated due to the patient's altered mentation.) The patient started to show improvement, and on Day 14, an immunofluorescence antibody (IFA) assay revealed *Rickettsia typhi* IgM titers 1:512 (< 1:64) and IgG titers 1:256 (< 1:64), consistent with a diagnosis of murine (endemic) typhus.

CONTINUED

➤ Serologic testing with IFA is the preferred diagnostic method; however, a definitive diagnosis is not needed before treatment can be started.

DISCUSSION

Murine typhus is an acute febrile disease caused by *R typhi*, an obligate, intracellular gram-negative organism.¹ Worldwide, transmission to humans occurs mainly from infected rat fleas harbored by rodents. In the United States, it's been suggested that opossums serve as an important reservoir in peridomestic settings, with cat fleas as vectors.²⁻⁴ The disease is endemic to southern California and south Texas.⁴

■ **Incidence of murine typhus** has declined in the United States since 1945 with the use of the insecticide dichlorodiphenyltrichloroethane (DDT). However, a recent rise in murine typhus cases—likely due to ecological changes—makes timely diagnosis and treatment essential.⁵ An epidemiologic study of 1762 confirmed cases in Texas from 2003 to 2013 found an increase in the number of cases and an expansion of the geographic areas impacted.³ Thus, in the work-up of acute fever of unknown origin, it is not unreasonable to include murine typhus in the differential.

Murine typhus can be difficult to diagnose due to nonspecific clinical manifestation.^{3,4} A 2016 systematic review of 2074 patients reported common symptoms of fever, headache, malaise, chills, and myalgia.⁶ The most common laboratory abnormalities in adults were elevated aminotransferases, lactate dehydrogenase, hypoalbuminemia, and thrombocytopenia.⁶ A 4-fold increase in typhus group IgM or IgG-specific antibody titer by IFA is supportive of diagnosis.⁴

■ **The differential diagnosis** included urosepsis, prostatitis, syphilis, HIV, and meningitis. However, lack of response to broad-spectrum antibiotics and antifungals made a diagnosis of urologic infection unlikely. A negative sexually transmitted infection screen ruled out syphilis and HIV. An incidental, elevated INR and delirium prevented us from obtaining a lumbar puncture to test for meningitis.

Treatment may begin without a definitive diagnosis

Serologic testing with IFA is the preferred diagnostic method; however, a definitive

diagnosis is not needed before treatment can be initiated. Doxycycline is the first-line therapy for all rickettsioses. Adults are advised to take doxycycline 200 mg orally once, followed by 100 mg twice daily until the patient improves, has been afebrile for 48 hours, and has received treatment for at least 7 days.⁷ Oral chloramphenicol is considered a second-line treatment; however it is not available in the United States and is associated with adverse hematologic effects.⁷

■ **Our patient** responded remarkably well to the doxycycline. After a 14-day course was completed, he was discharged to a skilled nursing facility for physical rehabilitation.

THE TAKEAWAY

Rickettsia diseases, such as murine typhus, should be considered in the differential if a patient presents with a worsening clinical picture of unresolved delirium; fever despite use of broad-spectrum antibiotics, antifungals, and antivirals; and a history of potential outdoor exposure. Sources include opossums or cats when flea contact is likely. Rickettsia diseases belong in the differential when there is a history of travel to tropical areas, as well. All suspected cases should be reported to the local health department.

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