CASE REPORTS

Suspected Typhus in a Pediatric Patient with Fever of Unknown Origin

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Murine typhus, caused by Rickettsia typhi, is an increasingly recognized but frequently underdiagnosed cause of pediatric febrile illness in endemic regions of the southern United States. Nonspecific symptoms and limitations of early serologic testing often delay diagnosis and treatment. We report the case of a previously healthy 12-year-old girl from South Texas who presented with five days of fever, headache, rash, gastrointestinal symptoms, leukopenia, normocytic anemia, elevated inflammatory markers, and mild transaminitis, with significant flea exposure. Initial rickettsial serologies were negative, and respiratory PCR was positive for rhinovirus/enterovirus; however, the overall clinical and epidemiologic picture raised strong concern for murine typhus. Empiric doxycycline therapy was initiated, resulting in rapid defervescence and clinical improvement. This case underscores the importance of considering murine typhus in children with fever and cytopenias in endemic areas, recognizing the limitations of early serologic testing, and initiating prompt empiric doxycycline to reduce morbidity and prevent complications.

BRIEF BACKGROUND

Murine typhus is increasing in recognition as a cause of acute febrile illness in the Southern U.S., particularly in Texas and California.[1] Despite its presence in those regions, it is often underdiagnosed due to the non-specific clinical presentation that often appears similar to viral illnesses or common infections. The number of reported cases of murine typhus in Texas has greatly increased in the last 20 years, particularly in suburban and rural areas of the state, which have large populations of opossums, cats, and their fleas; specifically, Ctenocephalides felis are the primary reservoirs and vectors of this bacterium.[2]

Diagnosis of rickettsial disease continues to be difficult, particularly in children. The early manifestations of fever, headache, fatigue, and gastrointestinal symptoms are all non-specific and can appear to mimic either viral gastroenteritis or viral respiratory infections.[2] A rash is a known manifestation of rickettsial disease; however, it may not appear or will be very subtle in many patients early in the disease process, making diagnosis even more complicated.[2] Many laboratory tests can suggest that a patient may have

a rickettsial disease through laboratory abnormalities, i.e., leukopenia, anemia, thrombocytopenia, transaminitis, and elevated inflammatory markers; however, they also lack specificity.[2]

A major limitation in diagnosing murine typhus is that diagnosis relies on serologic testing. The IFA is the standard method used to diagnose rickettsial disease, and unfortunately, most patients' IFAs will be negative until at least 7-10 days into the disease process due to a delay in the production of antibodies. Therefore, serologic testing alone is not sufficient to confirm the diagnosis, and a convalescent serum sample collected 2-4 weeks post-symptom onset showing a four-fold increase in IgG titer is usually needed, and as a result, treatment decisions are usually made based on the clinician's suspicion and the epidemiological context of the patient.[3]

Murine typhus can lead to serious complications, including pneumonia, meningitis, septic shock, and multiorgan failure. Treatment with doxycycline (Vibramycin) has been demonstrated to decrease the duration of fever and the length of time spent hospitalized, especially if initiated before 24 hours post-presentation.[4] Therefore, delaying both the diagnosis and treatment of murine typhus can result in increased morbidity and longer periods of illness.[3-5]

We present the case of a 12-year-old female from South Texas who presented with fever, rash, and cytopenias and received empirical treatment for murine typhus despite having negative initial serologic results. This case highlights the need to recognize rickettsial disease in endemic regions, understand the limitations of early serologic testing, and initiate doxycycline therapy promptly based on clinical suspicion.

CASE REPORT

A previously healthy 12-year-old girl from South Texas presented to the emergency department with five days of fever, headache, malaise, chills, generalized myalgias, nausea, vomiting, and non-bloody diarrhea.

Three days prior, she had been evaluated at an outpatient clinic, diagnosed presumptively with gastroenteritis, and prescribed azithromycin without improvement. Her epidemiologic history was notable for living in a semi-rural area with household pets (a dog and a cat), outdoor chickens, and a persistent flea infestation on the family dog.

On presentation, the patient appeared ill but not toxic, with moderate dehydration and facial thinning per parental report. Vital signs were hemodynamically stable, though she had experienced intermittent fevers up to 102°F (38.9°C). Physical examination revealed dry mucous membranes and a papular rash on the bilateral inner thighs, in the setting of chronic, recurrent "pimple-like" lesions on the lower extremities. There was no lymphadenopathy, meningismus, or hepatosplenomegaly.

Initial laboratory evaluation showed significant hematologic abnormalities, including leukopenia (WBC 1.9 × 10^3/μL; absolute neutrophil count 1.2–1.5 × 10^3/μL) and normocytic anemia (hemoglobin 10.4 g/dL, mean corpuscular volume 82.2 fL), with preserved platelet count (234 × 10^3/μL). Inflammatory markers were markedly elevated, with C-reactive protein of 16.2 mg/dL, erythrocyte sedimentation rate of 86 mm/hr, and mildly elevated procalcitonin at 0.48 ng/mL. The comprehensive metabolic panel demonstrated mild hypoalbuminemia and mild transaminitis, with normal lactate dehydrogenase.

Respiratory multiplex PCR was positive for human rhinovirus/enterovirus and negative for SARS-CoV-2, influenza, respiratory syncytial virus, and atypical pathogens. Urinalysis showed proteinuria, ketonuria, microscopic hematuria, and pyuria; urine culture later grew mixed gram-positive flora, suggesting contamination. Iron studies revealed iron deficiency with iron 3 μg/dL, transferrin saturation 1%, and mildly elevated ferritin (117.5 ng/mL), consistent with anemia of inflammation with superimposed iron deficiency.

Given the prolonged fever, rash, bicytopenia, elevated inflammatory markers, mild transaminitis, and residence in a murine typhus–endemic area with flea exposure, empiric intravenous doxycycline was initiated for suspected rickettsial infection. Ceftriaxone was added for a possible urinary tract infection, and the patient was admitted for monitoring. Overnight, she developed intermittent fever, hypothermia, and bradycardia, prompting escalation to cefepime while continuing doxycycline.

Serial complete blood counts demonstrated persistent leukopenia with a nadir of 1.3–1.4 × 10^3/μL and progressive normocytic anemia (hemoglobin 8.9–9.0 g/dL), with stable platelets and low reticulocyte counts (0.3–0.5%). Peripheral smear showed no blasts or atypical cells. Hematology/oncology consultation concluded the findings were most consistent with infection-associated bone marrow suppression, and bone marrow biopsy was deferred.

Rickettsial serologies for typhus group and Rocky Mountain spotted fever were negative, and blood cultures remained sterile; however, given the known limitations of early serologic testing, murine typhus remained the leading diagnosis. With continued doxycycline and supportive care, the patient's fevers resolved, inflammatory markers declined, and blood counts stabilized. She was discharged in good condition after completing oral doxycycline, with a working diagnosis of infection-related bone marrow suppression most consistent with murine typhus in the setting of concurrent rhinovirus/enterovirus infection.

DISCUSSION

This case illustrates the importance of considering vector-borne infections in children with fever, rash and cytopenias, even in the absence of confirmatory serology. Suspected typhus can mimic a viral illness and antibodies in serology

may not be detectable until later in the course of the illness, thus increasing morbidity if therapy is delayed. The patient's rickettsial tests were negative yet the team decided to treat empirically with doxycycline which ultimately improved her symptoms.

Typhus, specifically murine typhus, a disease caused by the vector-borne bacterium Rickettsia typhi, is a commonly missed cause of fever due to its nonspecific symptoms.[6] Typhus presents with fever and may present with varying additional clinical characteristics such as headache, rash, malaise, chills, myalgias, anorexia, nausea, vomiting, conjunctivitis, and lymphadenopathy.[6] Commonly observed laboratory findings include transaminase elevation, LDH elevation, hypoalbuminemia, elevated ESR, thrombocytopenia, anemia, hyponatremia, and leukopenia.[4] Presentation can differ in children compared to adults, with abdominal pain, diarrhea, and sore throat being more common symptoms.[6] In children, a laboratory tetrad is noted to consist of anemia, elevated ESR, transaminemia, and elevated LDH.[6]

Significant animal reservoirs of Rickettsia typhi include opossums and cats and within the United States, cases are concentrated within California and Texas.[7] The patient's exposure to domestic animals and a documented flea infestation represented recognized epidemiologic risk factors for murine typhus.

Pediatric fever with mild neutropenia presents a diagnostic challenge, as the differential diagnosis is broad and can include infectious, inflammatory, malignant, and hematologic conditions.[7] In the context of South Texas, other infectious considerations often include ehrlichiosis, cat-scratch disease (Bartonella henselae), or viral pathogens such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV), which can similarly present with cytopenias and transaminitis. Additionally, non-infectious etiologies like systemic lupus erythematosus (SLE) or Kawasaki disease must be considered when prolonged fever and rash are present.[2,5] The patient in this case presented with several clinical symptoms consistent with typhus including fever, headache, rash, myalgias, nausea, vomiting. While an LDH level was not obtained for this patient, she also had three out of the four findings in the above-mentioned pediatric laboratory tetrad - anemia, elevated ESR, and transaminemia. These findings, along with the known presence of typhus in South Texas, increased the concern for typhus in this patient.

Indirect immunofluorescence assay (IFA) is considered the gold standard for laboratory diagnosis of rickettsial diseases, including murine typhus.[6-8] However, a convalescent-phase specimen is often required, leading to delayed definitive diagnosis and false-negatives when blood specimens are collected

early on in the disease process.[5] For this reason, the treating team retained a high index of suspicion for typhus in this case despite negative typhus IFA results.

Tetracyclines, specifically doxycycline, are the treatment of choice for typhus. Appropriate treatment with a tetracycline is associated with significantly shorter time to defervescence.[4] While complications of typhus occur less frequently in children when compared to adults, complications observed in children include bronchiolitis, pneumonia, cholecystitis, myositis, and rhabdomyolysis.[6-8] In children over nine years of age, doxycycline is considered safe for the treatment of suspected rickettsial infection.[8] The course required for treatment is typically short, limiting the risk of dental staining in children.[8] The patient's fever resolved after three days of doxycycline treatment, indicating the successful treatment of presumed typhus.

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