

A case of glandular tularemia presenting with prolonged fever and mesenteric lymphadenopathy

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Tularemia is a zoonotic disease caused by *Francisella tularensis*, a gram-negative coccobacillus that is transmitted to humans by direct contact with or ingestion of infected animal tissues, through the bite of infected arthropods, by consumption of contaminated food or water, or from inhalation of aerosolized bacteria. Presented herein is a case of a four-year-old girl who was diagnosed with glandular tularemia after presenting with prolonged fever and mesenteric lymphadenopathy. A history of contact with a rabbit was a valuable clue for the diagnosis.

Key words: child, tularemia, mesenteric lymphadenopathy, prolonged fever.

Tularemia is an uncommon but potentially fatal zoonotic disease caused by the gram-negative coccobacillus *Francisella tularensis*. Although a wide range of animal reservoir hosts have been identified, it most commonly infects rabbits and rodents. Most reported cases of tularemia are from the northern hemisphere, most frequently in Scandinavia, Northern America, Japan, and Russia¹. However, several cases have also been reported in Turkey, Spain, and Switzerland^{1,2}. Tularemia is a growing threat in Turkey, and there has been a rise in the number of reported cases, both epidemic and sporadic, from different regions of Anatolia²⁻⁴.

Although the disease may have a silent and asymptomatic course, an infection may rapidly progress to sepsis and cause death if untreated. Several clinical forms have been described for tularemia: ulceroglandular (regional lymphadenopathy (LAP) and cutaneous ulcers), glandular (regional LAP without ulcers), oculoglandular (conjunctivitis and periauricular LAP), oropharyngeal (stomatitis, pharyngitis or tonsillitis with cervical LAP), typhoidal (fever without a localized sign or symptom in the early stage of the disease), and pneumonic (primary pleuropulmonary disease). Following a bite by an infected vector or skin contact with contaminated animal products, the most frequently encountered clinical forms are the glandular and ulceroglandular types¹.

Presented here is a case of a patient with prolonged fever and mesenteric LAP following contact with a rabbit, but with no history of a tick bite.

Case Report

An otherwise healthy four-year-old girl presented to the outpatient clinic of the Department of Pediatric Infectious Diseases with a 12-day history of fever (maximum measured temperature of 39.8°C), which peaked 3-4 times a day. She also had malaise, diaphoresis and cough. She had been evaluated in the emergency department six days earlier, where the presence of hyperemic tonsils prompted commencement of an oral course of amoxicillin-clavulanic acid pending the results of a throat culture, which was reported as negative.

The physical examination was unremarkable except for marked hyperemia of the oropharynx and tonsils and bilateral palpable cervical micro-LAPs. Laboratory tests revealed the presence of mild anemia (hemoglobin 11.4 g/dl), leukocytosis (26,700/mm³) and an elevated platelet count (620,000/mm³). Erythrocyte sedimentation rate was 81 mm/hour. Values on serum biochemistry were within normal range, with the exception of C-reactive protein and lactate dehydrogenase,

which were both elevated (4.8 mg/dl and 627 U/L, respectively). Serological tests for Epstein-Barr virus, cytomegalovirus, salmonella, and rubella were negative. Findings on echocardiographic examination were normal, whereas an ultrasound of the abdomen revealed the presence of multiple hypoechoic lesions, the largest of which was 34x19 mm in size, located on the right of the inferior vena cava at the level of the renal hilum, which were identified as mesenteric LAPs (Fig. 1). Evaluation by Doppler ultrasound showed the presence of a mild increase in vascularization. Citing a possibility of bacteremia, the patient was hospitalized and intravenous ceftriaxone treatment was initiated. No growth was detected on blood cultures. A history of contact with a rabbit at the girl's daycare center was uncovered after further questioning, which prompted testing for tularemia by a serum microagglutination test. The patient's fever broke on the fifth day of ceftriaxone treatment. Following a positive result for *F. tularensis* with a serum antibody titer of 1/1280, the patient was switched to intramuscular amikacin, which was continued for 10 days. A repeat ultrasound of the abdomen performed two weeks after completion of the treatment course showed that the previously enlarged mesenteric lymph nodes had shrunk, with the largest being 19x11 mm in size. Mesenteric LAPs had almost fully regressed one month later, and our patient was followed up for six months without any complaint.

Discussion

Recent years have witnessed an increase in the number of reported tularemia outbreaks



Fig. 1. Multiple mesenteric lymphadenopathies were seen in abdominal ultrasonography.

in several European countries^{1,5,6}. The ulceroglandular form of the disease, which is predominant in Spain, Sweden and Finland, has been reported to occur mostly as a result of arthropod bites⁶. In Turkey, on the other hand, the most frequently encountered form of tularemia is the oropharyngeal type⁴. Very few cases of glandular tularemia, which we believe is the type our patient had, have been reported from Turkey²⁻⁴, while reports from the United States most commonly describe the glandular form in both children and adults⁷.

A variety of small mammals, such as rabbits, mice, moles, and squirrels, are natural reservoirs for *F. tularensis*, and an infection is acquired through bites by ticks, flies and mosquitos or by contact with contaminated soil or water. The microorganism is transmitted to humans by direct contact with or consumption of infected animals or their tissues, by inhalation of dust contaminated by the feces of infected arthropods, or by drinking contaminated water^{1,5,7}. Our patient most probably acquired *F. tularensis* by direct contact with an infected rabbit. The rabbit was removed from the patient's daycare center after this event, but during this period, the rabbit showed no evidence of disease and no similar case was reported from the center.

Patients with tularemia usually present with an abrupt onset of fever and chills, headache, malaise, anorexia, and fatigue. Other reported symptoms include myalgia, chest discomfort, cough, vomiting, sore throat, abdominal pain, and diarrhea. Enlarged lymph nodes, which may be the initial and only sign of infection, are seen in nearly 85%, with cervical and periauricular lymph nodes being more frequently involved^{2,4}. In a report documenting the outbreak of tularemia in Turkey, LAP was present in 95.3% of patients, followed by fever in 83.7% and sore throat in 79.1% of patients². Our patient had prolonged fever, a frequently described finding of tularemia in the literature, without obvious cervical or periauricular LAP. Enlarged mesenteric lymph nodes were detected on abdominal ultrasonography requested as part of a work-up for fever of unknown origin. We are unaware of any report in the English literature of a tularemia case that presented with mesenteric LAPs and prolonged fever. However the mechanism of the disease is considered, this presentation is probable in tularemia.

Mesenteric LAPs in children are associated with a variety of conditions, such as infectious diseases, inflammatory lesions of the gastrointestinal system or malignant disorders⁸, although they may also be an incidental finding in asymptomatic children. In a study by Karmazyn et al.⁹ in a pediatric population, a short-axial diameter of less than 8 mm was considered normal. In another study by Grossman et al.¹⁰, it was concluded that the presence of a lymph node long-axial diameter of 10 mm or more merited further investigation. In our patient, ultrasound of the abdomen revealed the presence of LAPs of pathological size. However, as regression of LAPs and clinical improvement were observed at the end of the treatment, biopsy was not necessary.

Agglutinations tests detecting antibodies against *F. tularensis* in serum have traditionally been used to make a diagnosis of tularemia. However, detectable antibody response may take up to two weeks to manifest¹, and a diagnosis may not be possible with an agglutination test in the early stages of an infection. Nevertheless, a four-fold rise in microagglutination titer is considered diagnostic for tularemia infection. Although growth of the *F. tularensis* microorganism in the culture of infected material is the currently accepted gold standard for a diagnosis, this method requires special growth medium and sophisticated laboratory equipment, which may not be widely available. Furthermore, attempts to culture the microorganism pose a significant risk of infection for laboratory personnel. A diagnosis of tularemia was made in our patient after detection of *F. tularensis* antibodies at a titer of 1/1280 on an agglutination test, despite negative blood cultures.

F. tularensis is resistant to beta-lactam antibiotics¹¹, and treatment with such antibiotics may lead to a chronic disease process and delayed diagnosis⁴. On the other hand, a lack of response to beta-lactams in a patient empirically treated may be an important clue in the diagnosis of tularemia. Our patient's fever persisted despite 11 days of treatment with beta-lactam antibiotics (5 days of amoxicillin clavulanic acid and 6 days of ceftriaxone). Aminoglycosides, tetracyclines, chloramphenicol, and rifampin are the antibiotics that have been approved by the Food and Drug Administration for the

treatment of tularemia⁷. Early initiation of antibiotic treatment within the first week of an infection results in a significant reduction in the size of LAPs. Our patient responded well to amikacin with an obvious decrease in the size of the mesenteric LAPs two weeks after discontinuation of the treatment.

In countries such as Turkey, where tularemia is endemic, an infection may be acquired in several ways. Obtaining a detailed history is crucial for making a diagnosis, and a history of contact with animals, insect/rodent bite or consumption of possibly contaminated water or food may provide helpful clues. Prolonged fever and LAPs, either superficial or deep, are two major signs that are suggestive of tularemia. Early diagnosis and treatment of tularemia are very important due to the risk of progression to sepsis or even death.

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