FAMILIAL TULARAEMIA

Tularaemia is a zoonotic disease caused by Francisella tularensis. In this report, we have presented an early stage case of tularemia with fever and pharyngitis and two cases from the same non-endemic region with typical lymphadenitis. All three patients were treated with non-specific medications in healthcare centres, the treatment being directed towards symptoms resembling those of upper respiratory tract infections. However, there was no regression in their complaints. Because the first case had been treated earlier, his lymphadenopaties regressed and there was no suppuration. The other two cases, which had been suspected to be exposed to the same pathogen based on their histories, were at a mild acute phase and presented to our clinic with typical
lymphadenitis. The diagnoses of each of the three patients were made serologically. An early clinical recovery was achieved in the first patient with streptomycin (1 x 1 g/day im) and doxycycline (2 x 100 mg/day peroral) therapy. The therapy was prolonged to 4 weeks in the other two cases according to lymph node response and no complications occurring in their follow-ups. It can be concluded that tularemia should be considered in the differential diagnosis of patients with fever, pharyngitis, conjunctivitis and cervical lymphadenopathies that do not respond to β-lactam antibiotics.

**Key words:** Children, Francisella tularensis, treatment, tularemia

Tularaemia is a zoonotic disease caused by Francisella tularensis,[1,4] a small, fastidious, non-spore-forming, aerobic gram-negative coccobacillus. It is non-motile, non-piliated, and has a thin capsule composed mostly of lipid.[2] This bacterium was first identified in 1912 following reports of a plague-like illness in ground squirrels in Tulare County, CA. Since the discovery of this pathogen, four sub-species have been identified that exhibit distinct virulence and biochemical profiles as well as characteristic geographic distributions. Human disease is primarily associated with two F. tularensis sub-species: the highly virulent F. tularensis subsp. tularensis (type A), which is found only in North America, and the moderately virulent F. tularensis subsp. holarctica (type B), which is endemic throughout the Northern Hemisphere. Serovar B is less virulent, often results in subclinical infection, and has a worldwide distribution in the Northern hemisphere between latitudes 30 and 71 degrees north, including the continents of Europe, Asia, and North America.[3]

Tularaemia outbreaks have previously been reported in various geographical locations in Turkey. In this report, we report three cases from the same family that lived in the city of Bitlis in Turkey. This is first report from this non-endemic region.

**Case Reports**

**Case 1**

A 14-year-old male patient was admitted to our hospital in May 2007 with the complaints of high fever, malaise, chills, and generalized pain that had persisted for 3 days. On physical examination, the general condition was moderate. The patient was conscious and cooperative, the temperature remained in the range of 38–40.5°C, the heart rate was 82/min, and the arterial pressure was 110/70 mmHg. There was cervical lymphadenopathy in the neck. Apart from the discordance in pulses, the other physical systemic examinations were normal. The haemoglobin level was 14 g/dl, haematocrit was 43%, platelet was 136,000/mm³, and the erythrocyte sedimentation rate was 18 mm/h. The white blood cell count was 5900/mm³, with 80% polymorphonuclear cells and 20% lymphocytes. No atypical cells were observed. The Rose Bengal test was positive, but the Brucella standard tube agglutination test was negative. Therapy was begun with clindamycin, but the high fever persisted. Four days later, generalized cervical pain, swelling, hypersecretion, cough, and conjunctivitis were seen to have developed in the patient. There was no erythema or any other lesion on the body. Ultrasonography of the neck region revealed central cystic degenerative lymphadenopathy [Figure 1]. It was deduced from the detailed medical history that there was a history of swimming in a lake and sleeping on grass. His temperature remained in the range of 38–40.5°C. Doxycycline, in addition to streptomycin, was begun on the 5th day for suspected tularemia. The serum sample was analysed for the presence of F. tularensis antibody using a micro-agglutination test. The first result of the micro-agglutination test was negative. Six weeks later, the second test was determined positive, with a titre of 1:320.

**Case 2**

A 9-year-old male was admitted to our hospital 10 days after our first case, with complaints of fever and lymphadenopathy in the neck and the cervical regions. An antibiotic, cephradine, from the cephalosporins group, had initially been administered in the first medical centre that the patient had presented to. Physical examination revealed hypotrophy and hyperaemia of the tonsils in addition to painful lymphadenopathies, one in the upper cervical region measuring 4 x 3 cm in size and the other in the submental region of 3 x 3 cm size. We searched for similar cases in that region. There was a history of swimming in the same lake. The initial laboratory findings revealed a haemoglobin level of 12 g/dl, haematocrit of 35%, platelet count of 520,000/mm³, and erythrocyte sedimentation rate of 91 mm/h. The white blood cell count was 14,500/mm³, with 78% polymorphonuclear cells, 22% lymphocytes, and no atypical cells. The Rose Bengal test was positive, but the Brucella standard tube agglutination was negative. Ultrasonography of the neck showed a semi-solid area representing a lymph node [Figure 2]. Suspected for oropharyngeal tularemia, treatment was begun with doxycycline and streptomycin.

![Figure 1: Central necrotic–degenerative lymph node](image-url)
The micro-agglutination result was determined as positive at the titre of 1:1280. After treatment, the test was found to be positive, with a titre of 1:320.

Case 3

A 12-year-old male presented to our paediatrics department. His complaints had begun 17 days before admission, with a mass in the neck and the cervical region. An antibiotic from the cephalosporins family had been given in the first medical centre that the patient had presented to. He had history of swimming in the same lake. Physical examination revealed a hard, fixed, and painful lymphadenopathy of 3 x 3 cm size in the left upper cervical region. Laboratory findings were as follows: haemoglobin 13 g/dl; haematocrit 38%; platelets 387,000/mm³; erythrocyte sedimentation rate 80 mm/h. The white blood cell count was 10,000/mm³, with 68% polymorphonuclear cells, 32% lymphocytes, and no atypical cells. The result of the Rose Bengal test was positive, but the Brucella standard tube agglutination was negative. The bacterial culture of *F. tularensis* culture is not performed routinely in clinical laboratories. The laboratory diagnosis of tularemia is usually confirmed by a serum agglutination test using commercially available antigens. Thus, we used agglutination tests. However, as such in our patients, non-specific cross-reactions can occur in patients with brucella antibody. The diagnosis of brucella was found to be negative. The general condition of the patient improved and the lymphadenopathies regressed in 2 weeks of therapy. The next physical examination revealed no suppuration in the lymph node, with a significant reduction in lymphadenopathies. An agglutination titre performed on a blood specimen collected during the examination revealed a negative result (1:40), but a sample obtained 14 days later was positive, with a titre of 1:320.

Discussion

The clinical picture of tularemia may vary depending on several factors, such as the route of transmission, virulence of the microorganism strain, and the immune condition of the host. *F. tularensis* may enter the host through cuts or abrasions in the skin, by penetration through the mucous membranes of the eye, respiratory tract or oropharynx, or by percutaneous inoculation by arthropods. However, the most important source of *F. tularensis* transmission is the water supply because these bacteria may remain alive in water for several months. In our opinion, the water was contaminated with infected rodents. Because the patients had mentioned that they had played around the lake and also swam in that lake, we considered that the lake water had caused the disease and our hypothesis was supported by other patients who had not presented to the other departments of the hospital with similar symptoms. There is a probability that a ship may have sunk in that lake and, therefore, the children could have been infected. The reason for this consideration was that there were no patients who somehow had a connection with the lake water in the following days.

All our three cases were accepted as having oropharengeal tularemia. Most tularemia infections are acquired from contaminated water or food. There is direct invasion of the oropharynx by bacteria in the oropharengeal form. In these cases, the most important complaints were sore throat and fever. For this reason, it was confused with angina. Because of this confusion, non-specific antibiotic therapy had been administered to these patients. Clinical manifestations appear after an incubation period of 2–10 days. The most common clinical syndromes are ulceroglandular and glandular tularemia, which account for 80% of the reported cases. Recent cases have shown that the oropharyngeal type is more prevalent in our country. All these three cases were accepted as oropharengeal tularemia, and this is the first report from Bitlis in the east of Turkey.

The bacterial culture of *F. tularensis* culture is not performed routinely in clinical laboratories. The laboratory diagnosis of tularemia is usually confirmed by a serum agglutination test using commercially available antigens. Thus, we used agglutination tests. However, as such in our patients, non-specific cross-reactions can occur in patients with brucella antibody. The diagnosis of brucella was

---

**Figure 2:** Submental lymphadenopathy (A) and lymph node, including a semi-solid area progressing to cystic degeneration (B)
excluded using the brucella tube agglutination test, which was negative.

The cases were defined according to Centers for Disease Control and prevention (CDC) guidelines. The result of the sample blood of the first patient had turned out to be negative. The serum samples could be obtained from the patient during the early stages of infection. We think that this played a big role in explaining why the first sample was seronegative.

Streptomycin is accepted to be the drug of choice in tularaemia, but it is usually combined with the antibiotic doxycycline or chloramphenicol. \( F. \) \( tularensis \) is resistant to all \( \beta \)-lactam antibiotics. In the presented cases, the therapy of streptomycin (1 x 1 g/day im) combined with doxycycline (2 x 100 mg/day peroral) was given to all the patients according to the susceptibility data of Turkish isolates. It was determined that combined antibiotic therapy was effective and the therapy was prolonged to 4 weeks. Antibodies are generally detectable at the end of the second or during the third week of illness. Thus, empirical antibiotic therapy must be initiated before serological confirmation of infection.

The differential diagnoses include tuberculosis, sporotricosis, primary syphilis, pharyngitis of streptococcosis, infectious mononucleosis, adenoviral infections, cat scratch disease, and acute toxoplasmosis. These diagnoses can be excluded from the history of the patient, laboratory findings, and the symptoms on the physical examination.

It can be concluded that tularaemia should be considered in the differential diagnosis of patients with fever, pharyngitis, conjunctivitis, and cervical lymphadenopathies. Furthermore, early diagnosis and treatment of tularaemia are important to prevent abscess formation, and patients with delayed diagnosis may benefit from prolonged therapy.

References


*E Peker, A Ayaydin, N Duran

Mustafa Kemal University (EP), Medical Faculty, Department of Pediatrics, Hatay, Turkey, State Hospital (AA), Department of Microbiology, Bitlis, Turkey, Mustafa Kemal University (ND), Medical Faculty, Department of Microbiology and Clinical Microbiology, Hatay, Turkey

*Corresponding author: (e-mail: <pekererdal@hotmail.com>)

Received: 21-12-2008
Accepted: 19-02-2009

DOI: 10.4103/0255-0857.53217