

RESEARCH ARTICLE

## Epidemiological characteristics of tularemia cases in an endemic area

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### ABSTRACT

**Objectives:** We describe some characteristics (epidemiologic, clinical, diagnostic and treatment features) of the disease.

**Methods:** Epidemiological and clinical features of the patients with laboratory confirmed tularemia were reviewed retrospectively in Yozgat during two-year period.

**Results:** In total 13 patients with tularemia were included into this study. The mean age was  $33 \pm 15$  years (range 10 to 58), ten of them were female. The duration of complaints before admission to hospital was 12 days. As possible risk factors; two patients were living in endemic rural area; seven cases used natural water and eight cases consumed infected meat. Oropharyngeal tularemia was diagnosed in all cases. Sore throat, chills, fever and cervical mass were the most common complaints of patients. Nine cases had enlarged lymphadenopathies bilaterally. Ciprofloxacin and doxycycline combination was the most common treatment. The patients received therapy for up to 21 days and were considered successfully treated in the follow up. Death or serious complications were not observed.

**Conclusion:** Tularemia should be considered in patients presenting with lymphadenopathy, fever, sore throat and unresponsive to beta-lactam. Therefore, healthcare workers and community should be educated for the risk factors of the disease. *J Microbiol Infect Dis 2014; Special Issue 1: S58-S61*

**Key words:** Francisella tularensis, Tularemia, tonsillopharyngitis, lymphadenopathy, Yozgat

### Endemik bir bölgedeki tularemi hastalarının epidemiyolojik özellikleri

#### ÖZET

**Amaç:** Tulareminin endemik olduğu bir bölgede hastaların epidemiyolojik, klinik, tanısal, tedavi özellikleri araştırıldı.

**Yöntemler:** Yozgat bölgesinde iki yıllık süre içerisinde başvuran laboratuvar doğrulamalı Tularemi vakalarının epidemiyolojik ve klinik özellikleri retrospektif olarak değerlendirildi.

**Bulgular:** Çalışmaya toplamda 13 tularemi hastası dahil edildi. Yaş ortalaması  $33 \pm 15$  yıl bulundu. Hastaların onu kadını. Ortalama inkübasyon süresi 12 gündür. Risk faktörü olarak hastaların 2'sinde endemik bölgede yaşama, 5'inde hayvancılıkla uğraşma öyküsü ve 5'inde de kaynak suyu kullanım öyküsü bulunmaktadır. Olgularda en sık orofaringeal tularemi görülmektedir. En sık başvuru şikayetleri boğaz ağrısı, üşüme-titre, ateş, boyunda şişliktir. Hastaların dokuzunda bilateral, fluktuasyon veren lenf noduna rastlandı. Siprofloksasin+ doksisisiklin en sık kullanılan tedavi seçeneklerindedir. Cerrahi olarak lenf nodu drenajı yapıldı. Yaklaşık 21 gün süreyle tedavi alan hastalarda, tedavi açısından başarılı yanıtlar alınırken, ciddi komplikasyon gelişen, mortal seyreden vaka olmadı.

**Sonuç:** Özellikle servikal lenfadenopati, ateş, boğaz ağrısı ile başvuran ve beta-laktam tedavisine yanıtız hastalarda Tularemi akılda bulundurulmalıdır. Bu nedenle, hastalığın yönetimi açısından, sağlık personeli ve toplumun Tularemi ve risk faktörleri açısından eğitilmesi gerekmektedir.

**Anahtar kelimeler:** Francisella tularensis, Tularemi, Tonsillofarenjit, Lenfadenopati, Yozgat

#### INTRODUCTION

Tularemia is a zoonotic infection and disease is caused by Francisella tularensis.<sup>1</sup> Francisella is an aerobic, catalase positive, gram negative coccobacillus.<sup>2</sup> In recent years, tularemia has become an emerging infection in Turkey. Tularemia mostly

observed in rural areas and transmitted to humans by animal bites, contact with animal product, contaminated water, inhalation of infectious particles.<sup>3</sup> Patients with Tularemia are characterized with high fever pharyngitis or tonsillitis, regional enlarged and painful lymph nodes. The incubation period is 3-5 days.<sup>4</sup> The diseases may occur in different forms

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such as oropharyngeal, ulceroglandular, glandular, oculoglandular, pneumonic and typhoidal forms. Infections are generally presented as ulceroglandular forms in recent years. Oropharyngeal form is more common than the others.<sup>5</sup> The tetracyclines and fluoroquinolones are used as first line drugs for Tularemia.<sup>11</sup>

Yozgat is a province in central part of Turkey. Tularemia has become endemic in Yozgat. Since 2009, there have been 522 recorded laboratory confirmed cases of Tularemia cases in Yozgat. In this study, we describe the epidemiologic, clinical, diagnostic, treatment and prognostic features of the disease in a case series during last two years period.

## METHODS

Thirteen suspected Tularemia cases were admitted to the Department of Infectious Diseases, Yozgat State Hospital, between January 2011 and December 2012. Data were collected from medical records retrospectively. Data were included demographic characteristics of the patients, history of illness, symptoms, physical examination findings, clinical findings, laboratory results, treatment characteristics and therapeutic responses.

### Case definition

The Tularemia cases were diagnosed according to the World Health Organization case definition.<sup>6</sup> A suspected tularemia case was defined as a patient with the presence of fever, membranous pharyngitis or tonsillitis and cervical lymphadenopathy. Suspected cases may be come from the epidemic region and unresponsive to beta-lactam antibiotics. Suspected case with a positive serological laboratory result (serological titer  $\geq 1/160$  for micro-agglutination test) positive polymerase chain reaction (PCR) for *F. tularensis* was considered to be diagnosed with disease.

### Diagnostic Methods

Blood samples were taken from those having clinical findings consistent with tularemia. The serum parts of the blood samples were separated and sent to National Central Laboratory (Refik Saydam Hifzısıhha Center), Ankara, where the micro-agglutination test (MAT) was used for serological diagnosis. Confirmed tularemia cases were patients with compatible clinical findings and with positive serological titer ( titer $\geq 160$  for MAT).

## RESULTS

Thirteen patients diagnosed with tularemia were included in this study. We evaluated clinical features and laboratory findings of 13 tularemia cases. The mean age of the patients was  $33.0 \pm 15.1$  (10-58) years and 10 of them (76.9%) were female. Four (30.8%) patients had one of the following underlying health conditions (like diabetes mellitus, hypertension, and coronary artery disease) and one patient was pregnant. Demographic analysis of the cases, 46.2% of them lived in the rural area, 53.8% used naturel water and 61.5% consumed infected meat. The problems, associated with chlorination of water were noted in the some villages. Applications rates of chlorination were 14.2%. The duration of complaints until admission to hospital was 12 days (7-30 days). Oropharyngeal tularemia was diagnosed in 13 patients. Other forms were not diagnosed. The most common complaints of patients were sore throat (69.2%), fever (46.2%), chills (38.5%) and cervical mass (84.6%). Especially, about 69.2% (n=9) of the cases had bilaterally, 30.8% (n=4) of the patients had unilaterally enlarged cervical lymphadenopathies. Most of patients (69.2%) had misdiagnosed as acute tonsillitis before their admission to our clinic. They had a story that treated with beta-lactam antibiotics. Demographic and clinical features of the patients with Tularemia are seen Table 1.

**Table 1.** Demographic and clinical features of the patients with Tularemia

Variables	No (%)
Age (Mean) years (range)	30 (10-58)
Female, n (%)	10 (76.9)
Male, n (%)	3 (23.1)
Duration of symptoms (median $\pm$ SD, days)	12.00 $\pm$ 6.70
Places, n (%)	
City center, n (%)	1 (7.7)
County, n (%)	4 (30.8)
Village, n (%)	8 (61.5)
Type of water, n (%)	
Tap water, n (%)	6 (46.2)
Spring water, n (%)	7 (53.8)
Chlorination, n (%)	2 (15.4)
Tularemia story in the region, n (%)	6 (46.2)
Tularemia story in the family, n (%)	2 (15.4)

Increases of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell (WBC) were seen most frequently in the laboratory results. Laboratory findings of the patients with Tularemia are seen Table 2. Renal function tests were normal. Salmonella, Toxoplasma, Epstein Barr virus, Cytomegalovirus, hepatitis A/B/C, HIV serological tests were negative. Tube agglutination test for Brucella infection was positive in one patient. PPD (purified protein derivative) tests were negative. Chest radiographs were normal. Bacterial culture and tuberculosis tests of the lymph node drainage material were negative. Micro-agglutination test titers ranged between 1/160- 1/1280 in cases of Tularemia and 4 of the 13 patients in whom antibody titers were obtained by MAT had a 1/320 titer. Seven patients had 1/640, 1 had 1/1280, 1 had 1/160 titers.

**Table 2.** Clinical and laboratory findings of the patients with Tularemia

Cervical mass, n (%)	13(100)
Fever, n (%)	6 (46.2)
Chills, n (%)	5 (38.5)
Sore throat, n (%)	9 (69.2)
Conjunctivitis	0 (0)
Lymphadenopathy	
Right	3 (23.1)
Left	1 (7.7)
Bilateral	9 (69.2)
WBC (>12000/mm <sup>3</sup> )	6 (46.2)
ESR (>20 mm/saat)	7 (53.8)
CRP (>6 mg/L)	6 (46.2)
AST (>34 U/L)	1 (7.7)
ALT >49 U/L	1 (7.7)

While, 10 of 13 patients were treated with aminoglycoside, quinolone or the combinations of these antibiotics, three patients did not receive antibiotic treatment. One patient (7.7%) was treated with ciprofloxacin, one patient (7.7%) with streptomycin, one patient (7.7%) with streptomycin plus doxycycline. Seven patients were treated with Ciprofloxacin+ doxycycline was the most common treatment for patients. Brucella serological test was detected positive for one patient and treated with streptomycin+ doxycycline combination therapy.

Seven patients with extremely large lymph nodes and suppuration were hospitalized and surgical intervention was performed. Patient received the therapy for up to 21 days and they were considered successfully treated in the follow up. None of our patients died, and serious complications such as pneumonia, meningitis were observed in our patients.

## DISCUSSION

*F. tularensis* is a zoonotic infection. It is endemic disease and mainly seen in Turkey. Arthropods are the main transmission vectors.<sup>2</sup> Transmission occurs most often contaminated water and food, also contact with animal and tick bites are risk factors for transmission.<sup>7</sup> In our cases, 61.5% had a story of consumption of infected meat. The disease firstly had been reported from Luleburgaz town. After several outbreaks of tularemia have been reported other rural areas.<sup>4</sup> Since 2009 years there have been 522 recorded laboratory confirmed cases of Tularemia in Yozgat. Recent studies show that outbreaks were waterborne in our country.<sup>2</sup> In our region, the chlorination of water is a problem for some villages. In this study, applications rates of chlorination were 14.2%.

Tularemia has six clinical forms in humans in Turkey the oropharyngeal form was the most common.<sup>9,10</sup> In this study, oropharyngeal tularemia was diagnosed in 13 patients. Clinical presentation of tularemia and clinical signs vary between different clinical studies.<sup>11</sup> Dikici et al. retrospectively evaluated clinical features of 35 patients with tularemia in Konya region, Turkey and detected the most common complaints of cases were cervical mass (90%), sore throat (63%), chills (60%) and fever (58%).<sup>7</sup> In our cases, the most common complaints were sore throat (69.2%), chills (38.5%), fever (46.2%) and cervical mass (84.6%). The most frequently clinical findings were enlarged lymph nodes. About 69.2% (n=9) of the cases had bilaterally, 30.8% (n=4) of the patients had unilaterally enlarged cervical lymphadenopathies.

The gold standard test for diagnose is culture.<sup>12</sup> Positive culture for diagnosing Tularemia is best way, but isolation of bacteria is not routinely recommended. Usually, serological tests are used in the diagnosis. The growing bacteria is not a preferred way to diagnose the disease because of the difficulty of growing the bacteria and the high risk of infection in laboratory studies involving *F. tula-*

rensis.<sup>14</sup> Agglutination test and PCR are the most important tests among the non-culture methods. It is negative during the first two weeks following the onset of symptoms.<sup>11</sup> In our cases, the agglutination test was used to diagnose. High level micro-agglutination test titers of the cases could be related to the facts that the diagnosis disease was late and serum samples were obtained late.<sup>13</sup>

For decades, streptomycin, gentamicin and tetracycline have been used for the treatment of tularemia, but more recently quinolones have been considered as acceptable alternatives. Especially, ciprofloxacin have emerged as a new treatment option.<sup>5</sup> Antibiotics are used usually 2-3 weeks for treatment of Tularemia. But there was a high relapse rate in the present cases when using quinolone, tetracycline or combined therapy.<sup>8</sup> In this retrospective study, our patient were treated with aminoglycoside (streptomycin), quinolone (ciprofloxacin) or the combinations of these antibiotics, two patients not receive antibiotics. In these cases, pregnant women case did not receive antimicrobial therapy. Some patients with a diagnosis of suspected Tularemia admitted in the late period and despite the possibility of antimicrobial resistance, combined therapy (ciprofloxacin + doxycycline) was used for 7 (53.8%) patients. Helvacı et al. found that early antibiotic therapy (within the first 3 week) was much more effective for resolving the infection.<sup>15</sup> Çelebi et al. released a retrospective study on the efficacy of antibacterial therapy in the early period. In total 61 tularemia suspected cases were detected.<sup>13</sup> In this study, combination therapies were used. Especially, doxycycline plus ciprofloxacin therapy was used for 4(6.6%) patients, streptomycin plus doxycycline therapy was used for 36(59%) patients. However, within a 4-month period, 21 of 61 (34.4%) patients completely recovered from the illness. No mortality or major complications due to Tularemia was observed.<sup>13</sup> In our study, patient received the therapy for up to 21 days and they were considered successfully treated in the follow up. None of patients died, and serious complications were not observed.

The most important complication for tularemia patients is suppurations of lymph nodes. If the patients do not receive treatment may be self-draining.<sup>9</sup> In our cases, surgical intervention was

performed for seven patients with extremely large lymph nodes and suppurations.

In conclusion, tularemia should be considered in patients presenting with cervical lymphadenopathy, fever, sore throat and unresponsive to previous beta-lactam treatment. For this reason, healthcare personnel and community should be educated for the risk factors of tularemia.

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