CASE REPORT AND LITERATURE REVIEW /
OLGU SUNUMU VE LİTERATÜR TARAMASI

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Tularemia Associated with Natural Water Sources: Two Case Reports and Review of the Literature

Kaynak Suyu İlişkili Tularemi: İki Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Abstract

Tularemia is a rare zoonosis that is caused by *Francisella tularensis* and manifests with masses in the head and neck region. The most common form of tularemia is ulceroglandular form; the other clinical forms of tularemia are glandular, oculoglandular, pharyngeal, typhoidal, and pneumonic. The diagnosis of *F. tularensis* infection is made by serological, culture, or molecular methods. The epidemiological history should be thoroughly questioned and the necessary investigations should be planned with suspicion of tularemia for patients with lymphadenopathy (LAP) and history of contact with unregulated water sources. Although Trabzon is not an endemic area, we present two sporadic cases of oculoglandular and ulceroglandular tularemia in two brothers aged 59 and 57 years. Treatment with streptomycin for 14 days resulted in clinical improvement. Tularemia outbreaks associated with natural water sources in Turkey between January 1, 2000 and August 1, 2017 were screened and scrutinized using by the keywords "tularemi", "kaynak suyu", "LAP", "water resource", "tularemia", "lymphadenopathy" in PubMed, Google Scholar, and Web of Science. We determined that serologic methods are the most commonly used diagnostic method, the oropharyngeal form was the most common clinical form, and aminoglycosides were the most commonly used treatments, while ciprofloxacin and doxycycline are rarely used. There was no mortality except for one patient and there were not enough data about recurrence. Two cases of tularemia associated with natural water resources have been presented in this report. Even if patients do not come from endemic areas, tularemia should be considered in the differential diagnosis of LAP and targeted therapy should be planned.
Keywords: Water source, tularemia, lymphadenopathy, systematic review, treatment

Öz

Tularemi, *Francisella tularensis*'in neden olduğu nadir görülen bir zoonozdur. Hastalığın en sık görülen klinik formu ülseroglandüler form olup, glandüler, okuloglandüler, faringeal, tifoidal ve pnömonik olmak üzere altı farklı tabloda görülebilmektedir. Hastalığın tanısında kültür, seroloji ve moleküler yöntemlerden yararlanılmaktadır. Denetimsiz su kaynakları ile temas öyküsü bulunan, muayenesinde lenfadenopati (LAP) tespit edilen hastalarda epidemiyolojik öykü iyi sorgulanmalı ve tularemiden şüphelenilerek gerekli tetkikler planlanmalıdır. Bu yazıda, Trabzon endemik bölge olmamasına rağmen LAP etiyolojisi araştırılan 59 ve 57 yaşlarında okuloglandüler ve ülseroglandüler tularemi tanılarıyla on dört gün süreyle streptomisin tedavisi alıp klinik düzelme ile sonuçlanan iki sporadik olgu sunulmuştur. Ülkemizden 01.01.2000-01.08.2017 tarihleri arasında bildirilmiş su kaynaklı tularemi salgınları "tularemi", "kaynak suyu", "LAP", "water resource", "tularemia", "lymphadenopathy" anahtar kelimeleri kullanılarak PubMed, Google Scholar ve Web of Science taranarak irdelendi. Hastalık tanısında en sık kullanılan yöntemin serolojik yöntemler, en sık görülen klinik formun orofaringeal form olduğu ve tedavide en çok aminoglikozidlerin daha nadir olarak da siprofloksasin ve doksisiklinin kullanıldığı görülmüştür. Bir hasta dışında mortalite saptanmamış olup, olguların nüksüyle ilgili yeterli veri bulunamamıştır. Bu yazıda kaynak suyu ilişkili olduğu düşünülen iki tularemi olgusu sunulmuştur. Endemik bölgeden gelmese de epidemiyolojik öyküsü olan LAP'li hastaların ayırıcı tanısında tularemi düşünülmeli ve etkene dönük tedavileri planlanmalıdır.
Anahtar Kelimeler: Kaynak suyu, tularemi, lenfadenopati, sistematik derleme, terapi

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Introduction

Tularemia is a zoonosis caused by the Gram-negative bacterium *Francisella tularensis*[1-3]. In Turkey, tularemia usually occurs in the Black Sea and Marmara regions; epidemics are reported periodically, while the disease is encountered sporadically in other regions[2,4-15]. The disease is transmitted to humans by direct contact with infected animals, eating infected meat, via vectors such as ticks, or by contaminated water sources or inhalation of infectious aerosols. Human to human infection has not been documented[1-14].

The clinical presentation varies depending on the virulence of the agent, the route of entry into the body, the degree of systemic involvement, host immunity, and the timing of diagnosis and treatment. Average incubation time is 3 to 5 days, but can range from 2 to 21 days[1,3,16,17]. There are six clinical forms of tularemia: ulceroglandular, glandular, oculoglandular, pharyngeal, typhoidal, and pneumonic[1,3,17]. The ulceroglandular form is reported to be the most common worldwide (20-81%) [1,3,16,17]. Although the oropharyngeal form accounts for only 1% of cases globally, it is the most common form in Turkey[1-15].

Diagnosis is established by isolating *F. tularensis* in cultures of tissue or body fluid, serology, and molecular methods. Serologic tests may be negative in the first week of the disease and usually become positive after the second week. Tube agglutination and microagglutination (MAT) assays are the most commonly utilized serologic methods. Titers of ≥1/160 in the serum tube agglutination test, ≥1/128 for MAT, or ≥4-fold titer increase in serial measurements are diagnostically significant[1,3,17].

The first choice in antibiotic therapy for tularemia is streptomycin or gentamicin for at least 10 days. Alternatives are doxycycline and ciprofloxacin for 14 to 21 days[1,3,7,17,18].

In this paper, we report two related patients who presented with swelling in the neck after using the same spring water source, and who were diagnosed with tularemia while investigating the etiology of their lymphadenopathy (LAP). We discuss these cases in light of our literature review of reports from Turkey related to waterborne tularemia, identified by searching PubMed, Google Scholar and Web of Science for the keywords "tularemi", "spring water", "LAP", "water resource", "tularemia", and "lymphadenopathy".

Case Reports

Case 1

A 59-year-old male laborer, who had no known diseases and resided with his family in a rural area, presented with fever, fatigue, and swelling in the neck starting three weeks earlier. During this period, he had also developed burning, swelling, and redness in his right eye. He had seen another physician for his complaints, who prescribed amoxicillin-clavulanic acid 1 g twice daily. However, his symptoms did not improve and the treatment was changed to ciprofloxacin 500 mg twice daily and doxycycline 100 mg twice daily. The patient did not take the prescribed medication regularly or for long enough, and the antibiotherapy was not effective due to possible treatment noncompliance. The patient was directed to our clinic when his complaints increased. According to the history provided by the patient, he had been working at a construction site in Sivas three weeks before his symptoms appeared. It was learned that the drinking water at the site was obtained from a natural water source. Physical examination revealed painless, non-fluctuating, immobile, hard LAP about 2x2 cm in size in the parotid gland and cervical area, and hyperemia, edema, and conjunctivitis in the right eye (Figure 1). The other systemic examinations were normal. Laboratory test results were: erythrocyte sedimentation rate (ESR): 93 mm/h, C-reactive protein (CRP): 3.02 mg/dL, white blood cell count (WBC): 7.460/mL; other biochemical parameters were within normal limits.

Chest X-ray, HIV test, Epstein-Barr virus/cytomegalovirus serology, acid-fast bacilli (AFB) staining of sputum sample for tuberculosis (TB) and polymerase chain reaction (PCR) test for TB were conducted for differential diagnosis. All test results were negative. Ultrasound examination of the neck revealed a 21x11 mm LAP near the right internal jugular vein and a 25x19 mm LAP in the submandibular region. Histopathologic examination of an excisional biopsy sample was evaluated as granulomatous lymphadenitis and abscess formation. A serum sample was analyzed by MAT for tularemia in the Microbiology Reference Laboratory of the Turkish Institute of Public Health and the result was reported as 1/640. The patient was diagnosed with oculoglandular tularemia and was treated with intramuscular (IM) streptomycin 1 g daily for two weeks. Because antibiotic susceptibility is not analyzed in tularemia strains in our country, the antimicrobial

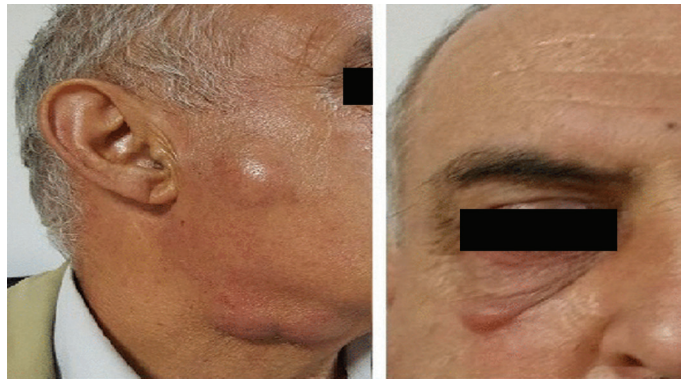

Figure 1. Oculoglandular tularemia

susceptibility of the agent could not be determined in our case. However, we believe our patient did not improve with ciprofloxacin and doxycycline treatment due to treatment noncompliance. The patient returned for follow-up 1 month after the treatment was completed. Physical examination showed that the cervical LAPs persisted, but the LAPs in the parotid gland were not palpable. The signs of conjunctivitis had completely resolved. No LAP was detected on palpation at 3-month follow-up.

Case 2

A 57-year-old male laborer, who was the brother of the first patient, presented with complaints of fever, fatigue, headache, and swelling in the neck beginning four weeks earlier. The patient had been empirically treated with clarithromycin (500 mg twice daily) for five days but was referred to our clinic when his symptoms failed to improve. The patient had history of going to Sivas to work with the first patient and drinking water from the same natural water source 3 weeks before his symptoms appeared. On physical examination, two painless, fixed, non-fluctuating LAPs approximately 3x2 cm in size were detected in the cervical region, while other systemic examinations were normal (Figure 2). Laboratory test results showed ESR: 30 mm/h, CRP: 1.49 mg/dL, WBC: 6.340/mL; other biochemical parameters were within normal limits. Chest X-ray, HIV test, Epstein-Barr virus/cytomegalovirus serology, AFB staining of sputum sample and PCR test for TB were conducted for differential diagnosis. All test results were negative.

Tularemia MAT test result was positive with a titer of 1/320, and the patient was diagnosed with ulceroglandular tularemia. He was treated with IM streptomycin 1 g daily for two weeks. None of the diagnostic tests for TB were positive. One month after the treatment was completed, the patient returned for follow-up with his brother. His cervical LAPs were still palpable on physical examination. No clinical signs were observed at follow-up 3 months later.

Figure 2. Ulceroglandular tularemia

Literature Review

Publications related to waterborne tularemia reported from our country between January 1, 2000 and August 1, 2017 were identified by searching PubMed, Google Scholar, and Web of Science using the keywords "tularemi", "spring water", "LAP", "water resource", "tularemia", and "lymphadenopathy". Fourteen articles were found, 11 of which were analyzed and summarized in Table 1.

Discussion

F. tularensis is the etiological agent of tularemia, a zoonosis with varying distribution throughout the world; the subspecies holarctica (type B) is responsible for outbreaks in Turkey. Waterborne outbreaks have been reported from the Thrace, Black Sea, and Marmara regions of Turkey[2,4,15]. Recently, 31 cases were reported in the Amasya region[6].

Table 1. Tularemia cases reported in Turkey

Author(s)	Number of cases	Clinical form	Mortality/ survival
Ulu Kılıç et al.[2]	15	Oropharyngeal Glandular Pneumonic	0/15
Sencan et al.[4]	22	Oropharyngeal Ulceroglandular	0/22
Akdoğan et al.[5]	25	Ulceroglandular	0/25
Uzun et al.[6]	31	Oropharyngeal	0/31
Gürcan[8]	431	Oropharyngeal	0/431
Uyar et al.[10]	10	Oropharyngeal	0/10
Ergin et al.[11]	29	Oropharyngeal Oculoglandular Glandular	0/29
Ozdemir et al.[14]	33	Oropharyngeal Ulceroglandular Oculoglandular	0/33
Akalin et al.[15]	1300	Oropharyngeal Oropharyngeal/glandular	1/1299
Helvacı[19]	205	Oropharyngeal Ulceroglandular Oculoglandular Glandular	0/205
Erdem et al.[24]	1034	Oropharyngeal Glandular Oculoglandular	0/1034

Tularemia is usually transmitted by direct contact with rodents or drinking and/or well water contaminated by rodents[1,3,9,17]. Our cases were infected probably through a contaminated drinking water source. Microorganisms may survive for months in drinking water. Although tularemia is not endemic in our city, the fact that the symptoms appeared after contact with a natural water source suggested that the etiological agent was water-borne. However, the water source was not investigated for the presence of the agent. Because there were no other cases from the same worksite at our hospital, we were unable to obtain information about the other workers. The patients that presented to our center were reported to the Communicable Diseases Unit of the Provincial Health Department.

The clinical presentation of tularemia varies depending on the route of *F. tularensis* infection. Oropharyngeal tularemia is the clinical form most commonly encountered in outbreaks in our country[2,4,15]. Oculoglandular tularemia is rare, accounting for 0-5% of cases[19]. The route of entry is the conjunctiva. The main symptoms are epiphora and photophobia. Our first case presented with ocular symptoms, and physical examination revealed a painful hyperemic lid lesion and conjunctival hyperemia in the right eye. The patient had a history of travel to an endemic area and had numerous cervical LAPs up to 42 mm in size on physical examination in addition to the other ocular findings, thus supporting oculoglandular tularemia. The other case was evaluated as ulceroglandular tularemia due to the presence of cervical LAP, fever, and headache. In our literature review, we also found reports of oculoglandular tularemia from Engin et al.[11], Helvaci et al.[13] and Ozdemir et al.[14]. In a report by Akalın et al.[15], the majority of the cases were oropharyngeal tularemia, and the oculoglandular form was not seen.

In routine practice, tularemia is usually diagnosed with serological tests[1,3,17]. These serological tests include tube agglutination, MAT, and hemagglutination tests and ELISA. The cases reported from Turkey were also diagnosed with serological tests. Another diagnostic method is real-time (RT)-PCR[1,3]. In a study by Ulu Kılıç et al.[2], two samples yielded positive cultures while five samples were positive according to PCR. Helvaci et al.[13] reported that bacteria were isolated in five seronegative cases. A definite diagnosis of tularemia is established by isolating the agent from body samples such as lymph nodes, wounds, sputum, blood, and pleural fluid[1,3,17,20,21]. However, due to the high virulence and contagiousness of the microorganism, culture is not recommended unless the necessary safety precautions are taken. Culturing should be done in laboratories equipped with biosafety level 2 or 3 facilities[1,17]. In our cases, MAT test was used for diagnosis. Tularemia is known to be one of the causes of granulomatous lymphadenitis[1-3,21], and histopathological findings supported the diagnosis in one of our cases.

The first choice of treatment is the antibiotic streptomycin, but tetracycline and quinolones may be used as alternatives. Moreover, some authors have suggested that streptomycin therapy can be combined with tetracycline, quinolone, and chloramphenicol[1-3,17,18,22,23]. Our review of the literature also revealed that the most commonly used agents were aminoglycosides, particularly streptomycin[2,4,6-8,10-15,18,19]. Helvaci et al.[13] reported using combinations with tetracycline or doxycycline. Amoxicillin-clavulanic acid, which was recommended to our first patient in a primary care center, is not a suitable treatment approach[1-3,7,13]. The clinical inefficacy of ciprofloxacin and doxycycline in our case is likely due to the inadequate treatment compliance. Early and appropriate treatment of tularemia results in reduction in lymph node size. However, suppuration and abscess of the lymph nodes have been reported in patients who are not treated within the first 2-3 weeks of infection[13,18]. With two weeks of streptomycin therapy, our patients did not develop suppuration; the lymph node enlargement persisted for a prolonged period, but no complications were observed.

In a multicenter study from Turkey; treatment failure was considered to have occured 48% of patients[24]. The most frequent reasons for failure were the production of suppuration in the lymph nodes after the start of treatment, the formation of new lymphadenomegalies under treatment, and persisting complaints despite two weeks of treatment[24].

In summary, tularemia is a rare infectious disease that causes masses to form in the head and neck region. It is encountered in Turkey as outbreaks or travel-related sporadic cases. Even if there is no history of travel to endemic areas, tularemia should be considered in the differential diagnosis of patients who exhibit periorbital edema and hyperemia and have LAP that does not respond to antibiotic treatment, and such cases should be treated accordingly.

Ethics

Informed Consent: Consent form was filled out by the reported cases.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Design: İ.K., H.N.K., Literature Search: H.N.K., F.A., S.K., G.Y., Writing: H.N.K., F.A., S.K.

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