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Epidemiological and clinical characteristics and management of oropharyngeal tularemia outbreak*

Mustafa Önder UZUN[1], Keramettin YANIK[2], Müge ERDEM[3], Uğur KOSTAKOĞLU[4], Gürdal YILMAZ[5], Yeliz TANRIVERDİ ÇAYCI[6,]**

[1]Department of Otorhinolaryngology, Çorlu Public Hospital, Tekirdağ, Turkey
[2]Department of Medical Microbiology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey
[3]Department of Infectious Diseases and Clinical Microbiology, Amasya Sabuncuoğlu Şerefeddin Public Hospital, Amasya, Turkey
[4]Department of Infectious Diseases and Clinical Microbiology, Trabzon Numune Training and Research Hospital, Trabzon, Turkey
[5]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey
[6]Department of Medical Microbiology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

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Background/aim: The purpose of this study was to determine the epidemiological and clinical characteristics of patients diagnosed with tularemia and the effectiveness of the administered treatments.

Materials and methods: Patients treated in our hospital between January 2009 and March 2011 and diagnosed with tularemia were evaluated retrospectively. Patients' epidemiological and clinical characteristics, administered treatments, and posttreatment findings were recorded on patient monitoring forms.

Results: At anamnesis, 29% of patients used water from wells and 71% used water from the network supply; moreover, 48.4% had a history of contact with animals and 87.1% a history of lethargy. At physical examination, 96.8% had a mass in the neck and 90.3% had fever. Gentamycin + doxycycline therapy was administered to 45.2% of patients, while levofloxacin, gentamycin, and streptomycin were used for the other patients. After treatment, neck masses persisted in 48.4% of patients and complaints of lethargy and fever in 6.5%. Treatment of these patients was initiated once tularemia had been diagnosed, as test results were announced about 3 weeks later. Lymphadenopathy excision was performed on 19.4% of patients in whom neck mass persisted.

Conclusion: Appropriate empiric antibiotherapy should be commenced in patients presenting with neck mass, fever, and lethargy in regions with tularemia epidemics.

Key words: *Francisella tularensis*, tularemia, epidemic

1. Introduction

Tularemia is a zoonotic disease caused by the bacterium *Francisella tularensis*. The infection is endemic in the northern hemisphere, including Turkey (1). Tularemia is prevalent in North America (*Francisella tularensis* subsp. *tularensis*), Europe (*Francisella tularensis* subsp. *holartica*) (particularly in Scandinavia), and Asia (including Russia and Japan) (1,2). The most common form of tularemia in these regions is the ulceroglandular form. Oropharyngeal tularemia is the most common clinical form of the disease in East Europe, including Turkey (2). *Francisella tularensis* is quite a resistant bacterium, surviving in humid and cold environments for weeks. However, it is not resistant to high temperatures and direct sunlight and cannot survive in chlorinated water (1). *Francisella tularensis* can infect warm-blooded and cold-blooded vertebrates and invertebrates and many kinds of arthropods. The wide range of reservoir hosts for humans includes primarily rodents, such as rabbits, mice, and squirrels, and secondarily raccoons, cattle, cats, and dogs (1,2). Tularemia is transmitted mainly by arthropod vectors living on animals, such as ticks, and by consumption of contaminated food and water (3). Different routes of transmission from animals to humans create difficulties in taking the necessary control measures. The disease, occasionally leading to epidemics, causes some problems

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** Correspondence: yeliztanriverdi@gmail.com

in diagnosis. Leblebicioglu et al. (4) reported 86 tularemia cases from Amasya in 2008 and 75 cases from Havza-Samsun (a district near Amasya) in 2005–2007 (5). The seropositivity of tularemia in Turkey has been reported to be between 2.1% and 31% (6–8). The seroprevalence of tularemia has been determined as 29.2% in Amasya (unpublished data). Tularemia may be misdiagnosed and treated for long periods as an upper respiratory tract infection. Furthermore, the complications of the infection may lead to prolonged treatment and patient discomfort. Particularly in endemic regions, tularemia should be considered in differential diagnosis.

The purpose of this study was to discuss the demographic, clinical, and epidemiological features of oropharyngeal tularemia in patients living in rural Amasya, who were diagnosed in our clinic. This study reports a new series of cases.

2. Materials and methods

The study included 31 patients referring to our clinic with complaints of fever, sore throat, and swelling in the neck in the time period between January 2009 and March 2011. The demographic, clinical, and epidemiological features of these patients were studied retrospectively. Patients who referred to our clinic with "neck mass of unknown origin" were hospitalized for further examination and treatment. Excisional biopsy in 6 patients and fine needle biopsy in 12 patients were performed for histopathological and microbiological examinations. To determine the etiology of the unknown neck mass, serological and enzyme immunoassay tests for *Brucella* (Rose-Bengal, Wright tube agglutination, and Coombs anti-*Brucella* agglutination), *Toxoplasma gondii*, rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein–Barr virus (EBV), hepatitis A, hepatitis B, hepatitis C, and histopathological examinations were performed in a local state hospital laboratory. Upon clinical consideration of tularemia, serum and biopsy specimens of all patients were sent to the National Reference Laboratory (Ministry of Health, Refik Saydam Center of Public Health) for microagglutination test (MAT) and indirect immunofluorescence assay (IFA). Tuberculin skin tests were also performed.

Upon the increased number of cases of oropharyngeal tularemia, a team of doctors, including the infectious disease specialist of our hospital, screened the areas where our patients lived for tularemia. This team made a total of 8 visits to these areas for exploration, specimen collection, and training people in taking preventive measures. The team invited individuals with a sore throat, fever, and/or swelling in the neck to our hospital for diagnosis and treatment. The potential environmental factors for epidemics were assessed. Specimens were collected from the main water system, well water, and spring water in the areas screened, and were then sent to the Public Health Laboratory of the Provincial Directorate of Health for microbiological examination. Those patients showing a MAT titer of 1:160 or above were included in the study.

3. Results

A total of 31 patients (19 females, and 12 males) were diagnosed to have oropharyngeal tularemia. The areas where the patients lived are shown in Table 1. The mean age of the patients was 33.1 ± 18.3 (3–67) years. The serological tests for *Brucella*, *T. gondii*, rubella, CMV, HSV, and viral hepatitis were negative for acute infection. Tularemia MAT results were positive at a titer of 1:160 in 16 patients (52%), 1:320 in 4 patients (13%), 1:640 in 1 patient (3.2%), and 1:1280 and over in 10 patients (32.3%). IFA results of biopsy specimens were determined as positive for 13 patients (13/18). The demographical, epidemiological, and clinical features of the patients with oropharyngeal tularemia are shown in Table 2. The most frequent complaints of the patients were mass in the neck, sore throat, and fever. Their complaints had started 13.4 ± 5.8 days before their referral to the hospital. Eight patients referring to the hospital at the beginning of the epidemic had received different diagnoses (acute tonsillitis, suppurative lymphadenitis, brucellosis, etc.) and had been treated with beta-lactam antibiotics; in the same period, 6 patients had also been prediagnosed with tuberculous lymphadenitis or malignancy. Among these misdiagnosed patients, the subjective complaints had decreased with antibiotic therapy in 5 patients, yet the masses in the neck had not regressed. For antibiotic therapy, gentamicin was used in 23 patients (74.2%), levofloxacin in 3 patients (9.7%), doxycycline in 3 patients (9.7%), and streptomycin in 2 patients (6.5%). Surgical drainage and surgical excision were performed for 12 (38.7%) and 6 (19.4%) patients, respectively. In all patients histopathology revealed no malignancy, although it did reveal "suppurative inflammatory reaction". In epidemiological assessment, 22 patients reported drinking main system water and 9 reported drinking well water. In addition, all patients reported drinking water from various public fountains in their villages. Fifteen patients (48.4%) had a history of contact with rodents or with their feces, and 6 patients (19.4%) had a history of tick bite. Twenty-eight of the patients (90.3%) were village dwellers. The

Table 1. Distribution of patients in terms of sex and localization.

Localization	Males n (%)	Females n (%)
City (n = 3)	2 (6.4)	1 (3.3)
Rural areas (n = 28)	10 (32.3)	18 (58)

Table 2. Demographical, epidemiological, and clinical characteristics of patients with oropharyngeal tularemia.

Variables	n (%)
Age, years (mean ± SD)	33.1 ± 18.3
Female	19 (61.3)
Days from symptom onset to first presentation (mean ± SD)	13.4 ± 5.8
Epidemiological characteristics	
Living in rural areas	28 (90.3)
Use of well water	9 (29)
Use of tap water	22 (71)
Consumption of contaminated water	20 (64.5)
Contact with rodents	15 (48.4)
Tick bites	6 (19.4)
Symptoms and signs	
Sore throat	29 (93.5)
Fever	28 (90.3)
Headache	16 (51.6)
Myalgia	12 (38.7)
Swelling on the neck	30 (96.8)
Lymphadenopathy	30 (96.8)
Cervical (unilateral)	20 (64.5)
Cervical (bilateral)	11 (35.5)
Submandibular (unilateral)	9 (29.0)
Lymphadenopathy >3 cm	22 (71.0)
Lymphadenopathy >5 cm	8 (25.8)
Tonsillopharyngitis	17 (54.8)
Laboratory findings	
Anemia	23 (74.2)
Leukocytosis (WBC count ≥10,000/μL)	13 (41.9)
Thrombocytopenia (platelets <150,000/μL)	1 (3.2)
High erythrocyte sedimentation rate	12 (38.7)
High erythrocyte sedimentation rate	15 (48.4)
Elevated liver enzymes	6 (19.4)

most significant epidemiological findings were that animal husbandry was the most common means of livelihood in these areas, and that there had been increased rodent activity around the villages, as reported by the village dwellers. In the villages where tularemia was found, the main water system was not regularly chlorinated. Well water had never been chlorinated. In 28.4% of the water samples, coliform bacilli were detected, but *F. tularensis* was not found in any of the samples.

4. Discussion

Tularemia is a zoonotic disease mainly of rodents, as well as of other animals and humans, presenting with different clinical features. Geographically, tularemia is limited to northern hemisphere countries (latitudes between 30°N and 71°N) (9,10). Tularemia is endemic in Europe, especially in Finland and Sweden. There have been reports on single cases and epidemics of tularemia in Austria, Germany, Spain, Hungary, and Bulgaria (11). In Turkey, the cases reported are mainly those of oropharyngeal tularemia patients because of waterborne outbreaks seen in recent years (1,2,11). In our study, all patients had oropharyngeal tularemia. In the oropharyngeal form of the infection, the lesions are located in the head and neck, and the primary complaints of the patients are sore throat, fever, and mass in the neck (11). Likewise, on their first visit to our clinic, all of our patients had hard/fixed masses in the neck of 2–9 cm in size. The patients were hospitalized with the prediagnosis of "neck mass of unknown origin". All patients were questioned in detail about their age, sex, profession, home address, hobbies (hunting, etc.), date when their complaints started, time length of complaints, therapies received, regression of complaints or lack thereof, other complaints besides those related to neck mass, growth rate of mass, risk factors for head and neck cancer, fever, pain, weight loss, night sweats, and past infections (tuberculosis, etc.). Open biopsy was performed for 6 patients and needle biopsy was performed for 12 patients for differential diagnosis; the rest of the patients were examined microbiologically for the presence of tularemia and other infections. All patients had high titers (≥1/160) of *F. tularensis*-specific antibodies as determined by MAT. Oropharyngeal tularemia is usually diagnosed at the time of the epidemic, because at the initial stage it does not have specific clinical and laboratory features (11). This form of tularemia may be confused with tonsillitis, pharyngitis, or cervical lymphadenitis caused by other microbial agents.

It is remarkable that the infection may also be present in family members or in persons in close circles of oropharyngeal tularemia patients, a situation that should lead to the diagnosis of an outbreak. All of our patients came from the same region and were relatives. This finding contributed to determining the tularemia outbreak. For this reason, in patient history-taking, the patient should also be questioned about similar complaints in family members and friends, water chlorination, environmental conditions, contact with animals, and consumption of game meat.

The infection sources for oropharyngeal tularemia are contaminated water and food (12,13). Our patients claimed that most of the water they used was not regularly chlorinated. The presence of coliform bacilli in 28.4% of the examined water samples supported this claim. Furthermore, almost half of our patients had a history of contact with rodents and rodent droppings. All these situations were risk factors for the development of tularemia. Although the source of contamination could not be clearly identified, the epidemic was controlled by public training, chlorination of water sources, and general cleaning of the environment with the help of the Provincial Directorate of Health.

The reports in the literature show that beta-lactam antibiotics are not effective in the treatment of tularemia cases. Suppuration in lymph nodes may continue in spite of empirically started antibiotics. Such suppuration under similar conditions may also be seen in streptococcal tonsillitis, EBV mononucleosis, and tuberculous lymphadenitis. Delay in the therapy of tularemia increases the probability of suppuration (9,12). In our study, 6 patients had initially received beta-lactam antibiotics for therapy, but had attained no recovery and no regression in the swellings in the neck.

Since oropharyngeal tularemia does not initially have specific clinical and laboratory features, it is usually diagnosed at the time of outbreaks. This form of the infection is readily confused with tonsillitis, pharyngitis, or cervical lymphadenitis caused by other microbial agents. This clinical form should be differentiated from viral infections causing unilateral lymphadenitis (EBV, CMV, rubella), from acute bacterial lymphadenitis (*Staphylococcus aureus*, *Streptococcus pyogenes*, Group B streptococci, anaerobes, *Pasteurella multocida*, *Yersinia pestis*, *Haemophilus influenzae* type b, etc.), from subacute and chronic lymphadenopathies [*Mycobacterium tuberculosis*, cat scratch disease, fungal infections (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*), parasites (*T. gondii*), and opportunistic infections], and from noninfectious diseases such as sarcoidosis and Kawasaki disease (11,14). It should be remembered that tularemia might also mimic a chronic granulomatous infection; in such cases, tularemia should be considered in differential diagnosis in order to not miss sporadic cases. In the management of tularemia, the first-choice antibiotics are streptomycin and gentamicin (12). Aminoglycoside treatment is recommended to continue for at least 10 days. Oral doxycycline and ciprofloxacin are the other treatment alternatives for adults and children and should be administered for 14–21 days (11). Our patients were treated with aminoglycosides, doxycycline, and quinolones. Additionally, 6 patients had to undergo surgical excision because of very enlarged lymph nodes.

In summary, tularemia is a zoonosis transmitted by drinking contaminated water, consuming contaminated food, inhaling contaminated aerosols, and by contact with infected animals. The correction of environmental conditions and regular chlorination of water sources

are significant measures in prevention. The diagnosis of tularemia starts with suspecting the presence of the disease. In endemic regions, tularemia should be considered in the differential diagnosis of tonsillopharyngitis plus a mass in the neck refractory to empirical antibiotic therapy. It is of utmost importance to assess the source of the infection even in the case of a single diagnosed patient. Determining the source of infection would greatly contribute to the prevention of possible outbreaks.

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