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Diagnosis of tularemia in a university hospital in Türkiye - 11-year evaluation

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Abstract

Aim: *Francisella tularensis* is a Gram-negative coccobacillus and is the causative agent of tularemia, which is endemic in our country. The most common clinical form in Turkey is the oropharyngeal form. Sensitive lymphadenopathy is the most important finding, and fever, fatigue, and muscle and joint pain may occur in all clinical forms. Rodents such as rabbits, mice, and squirrels are the main reservoirs for humans, and the transmission is through contact with infected animal secretions and organs, contaminated water, and food. This study aimed to examine the socio-demographic, epidemiological, and clinical features of cases diagnosed with tularemia.

Materials and Methods: Among the 583 patients whose serum samples were sent with a preliminary diagnosis of tularemia between 2011 and 2021, tularemia microagglutination test result (MAT) ≥1/160 titer, 18 years and older cases were included in the study.

Results: A total of 24 tularemia cases were detected, with a mean age of 43.3±17 years, 10 (41.7%) were male, and 14 (58.3%) were female. The most common symptoms and findings among the cases were lymphadenopathy (LAP) (95.8%), fatigue (66.7%), sore throat, and high fever (58.3%), and the most common epidemiological history was living in a rural area (91.7%) and dealing with animal husbandry (66.7%), and 18 (75%) cases were referred to as oropharyngeal tularemia. More than half of the cases were detected between October and March.

Conclusion: Tularemia is one of the endemic diseases in our country, and the epidemiological history should be taken carefully and kept in mind in the differential diagnosis of lymphadenopathy. Since it is the first tularemia study conducted in Malatya, it shows the epidemiological characteristics of the region.

Introduction

Tularemia is a zoonosis endemic in our country, and its causative agent *Francisella tularensis* is a Gram-negative coccobacillus that is immobile, aerobic, does not form spores, and can multiply inside the cell. It is a zoonotic infectious disease in the Northern Hemisphere [1, 2]. The first epidemic in Turkey was seen in Lüleburgaz in 1936, and cases were reported in other regions in the following years [3, 4]. Rodents such as rabbits, mice, and squirrels are the main reservoirs for humans, and the transmission is through contact with infected animal secretions and organs, contaminated water, and food. It may present a clinical picture in the form of fever, weakness, muscle and joint pain, and painful lymphadenopathy. The most common clinical form in Turkey is the oropharyngeal form [1, 2, 5]. This study aimed to examine the clinical and laboratory findings of the cases diagnosed with tularemia in Malatya region between the years 2011-2021.

Materials and Methods

Between January 2011 and December 2021, 583 patients who applied to the Inonu University Faculty of Medicine Infectious Diseases and Clinical Microbiology Outpatient Clinic with complaints of fever, neck swelling and sore throat and whose serum samples were sent to the Public Health Institution Laboratory with a preliminary diagnosis of tularemia were retrospectively analyzed. Cases with a tularemia microagglutination test result (MAT) of ≥1/160 were considered serologically positive. A total of 24 patients with a diagnosis of tularemia were examined, by including patients aged 18 years and older with positive serological tests.

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The patients' age, gender, epidemiological history and risk factors (living in a rural area, dealing with animal husbandry, contact with rodents, travel history, tick attachment history, hunting animal history, use of water resources), clinical and examination findings, laboratory values , and treatments were analyzed retrospectively from the tularemia case inquiry form and the hospital automation system. Data including sociodemographic, epidemiological and clinical information were given as numbers (%). Laboratory values; leukocytosis was taken as $>10^4/mm^3$, C-reactive protein (CRP) elevation ≥1 mg/dL, elevated sedimentation rate ≥20 mm/hour. In addition, white blood cell (WBC), CRP and sedimentation values were calculated as mean±SD (min-max). The ethics committee approval of the study was obtained from the research ethics committee of Inonu University (2022/3467).

Results

In our study, samples were sent from 583 patients suspected of tularemia between 2011-2021. A total of 24 cases of tularemia, aged 18 years and over, with a tularemia microagglutination test result (MAT)≥1/160 titer were detected. The mean age of the cases was calculated as 43.3±17 years, 10 (41.7%) were male, and 14 (58.3%) were female. When the arrival places of the cases were examined, it was determined that there were 17 (70.8%) cases from Malatya, 5 (20.8%) cases from Muş, and 1 (4.2%) case from Adıyaman and Kahramanmaraş. 62.5% of the cases were detected between October and March.

The most common symptoms and findings among the cases were lymphadenopathy (LAP) (95.8%), fatigue (66.7%), sore throat, and high fever (58.3%), and the most common epidemiological history was living in a rural area (91.7% and dealing with animal husbandry (66.7%). Of the patients with lymphadenopathy, 87% had cervical LAP, 8.7% had submandibular LAP, and 4.4% had axillary LAP. 18 (75%) of the cases were oropharyngeal, 2 (8.3%) were glandular tularemia, and the data of 4 of them could not be reached. Demographic and clinical data of the patients in the study are given in Table 1.

When the distribution of tularemia cases by year is evaluated, the highest number of cases was observed, with 5 cases in 2017 (Figure 1). When the laboratory values of the patients were examined, leukocytosis was found in 29.2%, CRP elevation in 25%, and elevated sedimentation rate in 50% of the patients. The most commonly used antibiotic regimen in the treatment was doxycycline monotherapy, with 54.1%. Details are given in Table 2.

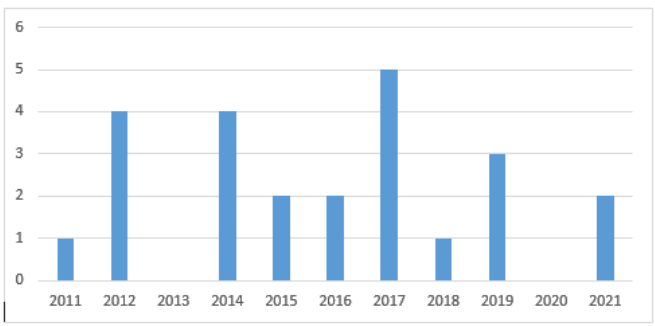

Figure 1. Tularemia cases by year.

Table 1. Demographic and clinical data of the patients in our study.

	n, (%)
Gender	
Female	14 (58.3)
Male	10 (41.7)
Age	
Mean±SD	43.3±17
Min-Max	17-77
Symptoms	n, (%)
Weakness	16 (66.7)
Sore throat	14 (58.3)
High fever	14 (58.3)
Muscle and joint pain	10 (41.7)
Sore in mouth	7 (29.2)
Redness in the eyes	5 (20.8)
Abdominal pain and/or diarrhea	4 (16.7)
Skin sore and/or rash	4 (16.7)
Nausea, vomiting	3 (12.5)
Epidemiological History	
Living in the countryside	22 (91.7)
Dealing with animal husbandry	16 (66.7)
Contact with a rodent or its feces, being around the house	12 (50)
Travel story	8 (33.3)
Contact with lake-stream water	7 (29.2)
Well water use	4 (16.7)
History of contact with or eating a game animal	2 (8.3)
Tick attachment history	1 (4.2)
Physical Examination	n (%)
Lymphadenopathy	23 (95.8)
Skin lesion	4 (16.7)
Fever (>38℃)	3 (12.5)
Tonsillopharyngitis	3 (12.5)
Oral mucosal lesion	2 (8.3)
Conjunctivitis	0 (0)

Discussion

Tularemia was first seen in our country in 1936 and continued to be seen in small-scale epidemics and sporadic cases in various regions over the years. It was included in the list of "notifiable diseases" by the Ministry of Health in 2005. Although it is mainly seen in the Marmara and the Black Sea Regions, it can be seen all over Turkey [1]. This study aimed to examine the Malatya region's tularemia cases between 2011 and 2021. No cases were detected in 2013 and 2020. Although it is thought that it may have been missed due to the decrease in hospital admissions due to the pandemic and deficiencies in the differential diagnosis in 2020, we cannot give an opinion on the reason why no cases were detected in 2013.

Table 2. Laboratory data of the cases and antibiotic regimens used.

Tularemia Micro-Agglutination Test	n (%)
1/160	1 (4.2)
1/320	4 (16.7)
1/640	13 (54.2)
1/1280	6 (25)
Laboratory values	
Leukocytosis, $>10^4/mm^3$	7 (29.2)
CRP elevation, $\geq$1 mg/dL	6 (25)
Elevated sedimentation rate, $\geq$20 mm/hour	12 (50)
WBC, $/mm^3$	
Mean±SD	8.4±2.1
Min-Max	4.3-12.8
CRP, mg/dL	
Mean±SD	1.5±2.8
Min-Max	0.3-13
Sedimentation rate, mm/hour	
Mean±SD	24.7±17.4
Min-Max	2-65
Antibiotics used in the treatment	
Doxycycline	13 (54.1)
Doxycycline+ciprofloxacin	3 (12.5)
Streptomycin	1 (4.2)
Ciprofloxacin	1 (4.2)
Patient not followed-up	6 (25)

Seroprevalence studies in tularemia are beneficial in determining whether the agent is present in that region and in determining risk factors [6]. A positivity rate of 9.7-19.7% was found in tularemia seroprevalence studies conducted in epidemic regions of Europe [7]. In a study conducted on hunters around Elazig, the tularemia seropositivity was found to be 3.3% [8]. Tularemia antibody positivity was found at a rate of 1.3% in a seroprevalence study conducted on blood donors in the Diyarbakir region [9].

Seasonal changes such as temperature and precipitation affect tularemia's spread and geographical distribution. Climatic temperatures and global warming have been the determining factors in the spread of rodent and vector-mediated infections [10]. It has been shown for the first time in Turkey that mice in the natural environment carry F. tularensis bacteria, the causative agent of tularemia [11]. In our country, there may be waterborne infections. Contaminated drinking water was reported to be the primary cause of a tularemia outbreak in southwestern Turkey. It has also been reported that the primary approach to preventing the epidemic is the improvement of appropriate water infrastructure and sanitation systems [12]. It has been reported that tularemia cases generally occur in autumn and winter periods in our country [1]. A study conducted in Yozgat province found that tularemia cases were most common in winter and spring [13]. In a reported study, 73.1% of the cases were seen between October and March [14], and similarly, in our study, more than half of the cases were found between October and March, which is the autumn-winter period.

Of the cases in our study, 91.7% lived in rural areas, 66.7% engaged in animal husbandry, 50% had a history of contact with rodents and being around the house, 29.2% contacted lake-stream water, and 16.7% had a history of well water usage. In a study conducted in the Konya region, it was reported that 73% of the cases had a history of contact with rodents and being in the home environment, 68% of them lived in rural areas, 53% had a history of animal feeding, and 25% had a history of contact with lake-stream water [15]. In another study conducted in the Eastern Anatolia Region, it was stated that 76.9% of the cases resided in rural areas, 65.4% were engaged in animal husbandry, and 53.8% had rodents in their living areas, and 34.6% used spring water [14]. In a study conducted in the Samsun region, it was stated that 93.8% used tap water, 75% lived in rural areas, 56.3% engaged in agriculture, 37.5% engaged in animal husbandry and the presence of rodents around 25% [16]. It is understood from our study and other studies that the risk factors are similar: living in rural areas, contact with rodents, use of natural spring water, and contamination of drinking water. In this study we conducted in the Malatya region, contamination from contaminated water was lower, and it was thought that living in rural areas, dealing with livestock, and contacting rodents were more risk factors.

It is seen more frequently over the age of 30 because risk group jobs such as contaminated water in the living area, house and its surroundings, contaminated food, and rodent animal extractions that may be a reservoir are performed mainly by adults and women [1]. In various studies conducted in our country, it has been observed that tularemia is more common in women than men [13, 15]. In our study, more than half of the existing cases were women. In the study of Alkan-Çeviker et al., the most common symptoms were enlarged lymph nodes (93.8%), sore throat (43.8%), fatigue (43.8%), and muscle and joint pains (43.8%), and the most common finding was lymphadenopathy [16]. In their study, Özden K et al. reported that the most common symptoms and findings were fever (88.5%), sore throat (92.3%) and in all of them, cervical lymphadenopathy (LAP) [14]. A multicenter study reported that 95% of the cases had lymphadenopathy, 85% had a fever, and 84% had sore throat and muscle pain [17]. In another study examining tularemia, the most common symptoms and findings were reported as LAP (91%), sore throat (68.9%), fatigue (68.9%), and fever (31.1%) [18]. In our study, similar to the literature, the most common symptoms and findings were lymphadenopathy, fatigue, sore throat, high fever, and muscle and joint pain.

In a study by Dikici et al., when tularemia forms were examined, oropharyngeal tularemia was diagnosed in 62.5% of the cases, and glandular tularemia in 22.5%, and oculoglandular tularemia in 7.5% [15]. In the study of Özden K. et al., all of the cases were evaluated as a form of oropharyngeal tularemia [14]. In another study, oropharyngeal involvement was reported in 62.5% of the cases, glandular involvement in 31.3%, and ulceroglandular involvement in 6.3% [16]. In other similar studies, oropharyngeal tularemia constitutes most of the cases in Turkey [19, 20,

21]. In our study, most of the cases were oropharyngeal tularemia.

Effective treatments commonly used in the treatment of tularemia are streptomycin, gentamicin, ciprofloxacin, and doxycycline [22]. The use of doxycycline is more common in some centers, and aminoglycoside use is more common in some centers. In a study, the most commonly used antibiotics in the treatment of tularemia were reported as streptomycin 28%, ciprofloxacin 18%, doxycycline 12%, gentamicin 8%, streptomycin + doxycycline 10%, ciprofloxacin + doxycycline 8% [17]. In another study, the most commonly used treatment regimen was 42% doxycycline, 20% ciprofloxacin + doxycycline, 14% streptomycin, and ciprofloxacin [23]. In the study of Alkan-Çeviker et al., streptomycin treatment was given to all tularemia cases [16]. In another study, aminoglycosides, ciprofloxacin, doxycycline, and their combinations were used most frequently [18]. In our study, mostly doxycycline, less frequently ciprofloxacin and streptomycin were used in treating tularemia cases.

Conclusion

This study is the first study of tularemia reported from the Malatya region. It should be known that tularemia is one of the endemic diseases seen in our country, not only in the Black Sea and Marmara regions but also in the Eastern Anatolia Region, such as Malatya, the epidemiological history should be taken carefully, and it should be kept in mind in the differential diagnosis of lymphadenopathy.

Disclosure

This study was presented as an oral presentation at the 9thSociety for the Prevention of Infectious Diseases (BUHASDER) Congress (24-28 November 2021).

Ethics approval

The ethics committee approval of the study was obtained from the research ethics committee of Inonu University (2022/3467).

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