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ORIGINAL ARTICLE – OPEN ACCESS

Retrospective Analysis of Tularemia Cases in Tokat, Türkiye

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ABSTRACT

Objective: Tularemia is a rare and often overlooked zoonotic infection. While the ulceroglandular and glandular types are observed most frequently in epidemics originating in Europe, the oropharyngeal type is most common in Türkiye. The most common clinical findings are lymphadenopathy, skin rash, and tonsillitis. The aim of this study was to investigate the frequency of tularemia in Tokat, a province located in the Central Black Sea Region of Türkiye.

Materials and Methods: The data of patients diagnosed with tularemia at Tokat Gaziosmanpaşa University Faculty of Medicine Training and Research Hospital between January 2011 and July 2021 were retrospectively analyzed. Laboratory-confirmed cases were included in the study. Sociodemographic characteristics, risk factors, clinical and laboratory findings, treatments, and post-treatment follow-up of the cases were evaluated.

Results: Tularemia was detected in 20 patients. A total of 80% patients lived in a village, 65% were engaged in agriculture as a profession, and 60% in animal husbandry. The most important possible sources of contamination were rodents near the house (40%) and non-chlorinated drinking water (50%). Among 20 cases, 57% were oropharyngeal tularemia, 95% were treated with monotherapy or combinations containing aminoglycosides, and 50% with surgical lymph node drainage.

Conclusion: Tularemia is a rare infection in Tokat Province. But it should be considered in the differential diagnosis of patients living in rural areas who present with fever, sore throat, and cervical lymphadenopathy that is not responsive to beta-lactam agents.

Keywords: Central Black Sea, *Francisella tularensis*, Tokat, tularemia

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INTRODUCTION

Tularemia is a zoonotic infectious disease caused by *Francisella tularensis*, a small, aerobic, Gram-negative coccobacillus. *F. tularensis* is an extremely contagious bacterium. It can spread to humans through the bite of an infected arthropod, contact with infected animal material, ingestion of contaminated food or water, or inhalation of contaminated aerosols (1). There are 4 subtypes: *F. tularensis subsp. tularensis* (type A), *subsp. holarctica* (type B), *subsp. mediasiatica*, and *subsp. novicida*. Type A is more commonly transmitted through a tick bite or rodent contact, whereas type B is more commonly transmitted through contaminated water or food (2, 3).

The clinical manifestations of tularemia may range from asymptomatic illness to septic shock and death, in part depending on the virulence of the bacterium, portal of entry, quantity of inoculum, and the immune status of the host (4). The infection typically manifests as regional lymphadenopathy and skin/mucosal ulceration following contact with infected animal material, pharyngitis and tonsillitis with lymphadenopathy following ingestion of contaminated food or water, or pneumonia and systemic disease following inhalation of contaminated aerosols (1, 4).

Tularemia is classified into 6 clinical forms according to the route of entry of the bacterium into the host. The ulceroglandular form is typically characterized by regional lymphadenopathy and cutaneous ulcer; the glandular form by regional lymphadenopathy without ulceration; the oculoglandular form by conjunctivitis and preauricular lymphadenopathy; the oropharyngeal form by cervical lymphadenopathy with stomatitis, pharyngitis, or tonsillitis; the pneumonic form by primary pleuropulmonary disease; and the typhoid form by febrile disease without early localized signs and symptoms. The ulceroglandular form is the most commonly reported worldwide (20–81%). Although the oropharyngeal form is seen at a rate of 1% worldwide, it is the most common clinical form of tularemia in Türkiye, with a rate of 77% (5).

Tularemia generally occurs only as sporadic cases in the Northern Hemisphere, but occasionally causes epidemics. However, the distribution of tularemia in the Northern Hemisphere is not homogeneous (6). The first recorded tularemia epidemic in Türkiye was in Lüleburgaz, in the Marmara Region, in 1936, and sporadic cases and small outbreaks were reported from different regions in the following years. The biggest

known tularemia epidemic in this country was seen in Antalya in 1953. Tularemia came to the fore again with the detection of an epidemic of 64 cases in Bursa Province, also in the Marmara region, in 1988, 35 years later. Previous studies have demonstrated that *F. tularensis* is endemic in Türkiye, primarily in the Marmara, Black Sea, and Central Anatolia regions, and typically causes small epidemics (6, 7) Tularemia is among the C group of diseases that since 2004 require reporting to Ministry of Health communicable diseases notification system (6).

Tularemia may be confused with many diseases and sporadic cases, in particular, may be missed. Therefore, it may be misdiagnosed and mistreated, leading to delay in the correct diagnosis and treatment (8). The objective of this study was to evaluate the epidemiological data, clinical findings, risk factors, and treatments of laboratory-confirmed tularemia cases between 2011–2021 in the province of Tokat, located in the Central Black Sea Region.

MATERIALS and METHODS

Ethical Considerations

This study was approved by the Clinical Research Ethics Committee of the Tokat Gaziosmanpaşa University Faculty of Medicine (no: 20-KAEK-189).

Study Design

This was an observational, descriptive study. The data of patients who applied to Tokat Gaziosmanpaşa University Training and Research Hospital between January 2011 and July 2021 and were diagnosed with tularemia were analyzed. Patient records were obtained from the automated hospital record management system and the General Directorate of Public Health Tularemia Information System.

Only laboratory-confirmed cases were included in the study. According to the US Centers for Disease Control and Prevention guidelines, isolation of *F. tularensis* from a clinical sample and seroconversion of antibodies to *F. tularensis* in serum samples taken at 2- to 3-week intervals were determined to be definitive diagnostic criteria. In addition, detection of antibodies to *F. tularensis* in a single serum sample or detection of *F. tularensis* in a polymerase chain reaction (PCR) test in patients with compatible clinical findings is also diagnostic (9). According to the Tularemia Field Guide of the Turkish Ministry of Health, in the presence of clinical suspicion and findings, the result of a tube agglutination test performed on a single serum sample of ≥1:160 is also diagnostic (6). In this study, laboratory-confirmed tularemia was defined as having at least 1 of the following criteria:

- Presence of antibodies to *F. tularensis* in the serum with a titer of >1/160
- Detection of *F. tularensis* with molecular test (PCR assay)
- Isolation of *F. tularensis* from clinical specimen

The sociodemographic characteristics of the patients (age, gender, occupation, place of residence, characteristics of water resources in rural areas), risk factors (animal contact, history of tick and/or rodent bites, etc.), clinical and laboratory findings, treatments, and post-treatment follow-up were noted and evaluated.

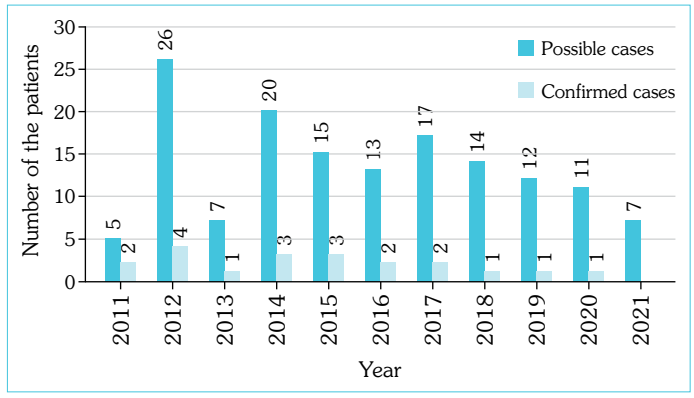

Figure 1. Distribution of tularemia cases according to year

The clinical presentations were categorized as ulceroglandular, glandular, oculoglandular, oropharyngeal, typhoidal, or pneumonic tularemia based on patient's symptoms and physical examination findings in the patient records.

Statistical Analysis

IBM SPSS Statistics for Windows, Version 22.0 software (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis. The conformity of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics were presented as numbers and percentages for categorical variables, mean±SD for normally distributed continuous variables, and median (minimum–maximum) for non-normally distributed continuous variables. The Pearson chi-square test and Fisher's exact test were used for comparisons of categorical variables. Variables were compared between groups using Student's t-test and the Mann-Whitney U test. A p value of <0.05 was considered statistically significant.

RESULTS

The diagnosis was confirmed in 20 (13.6%) of 146 patients with a preliminary diagnosis of tularemia. Thirteen (65%) of the patients were male and the mean age was 42 years (min–max: 4–81 years). The diagnosis was confirmed with detection of *F. tularensis* by PCR in 1 patient (5%) and antibodies to *F. tularensis* in 19 patients (95%).

Data of the year and season in which the cases were detected are presented in Figure 1 and Figure 2, and information about the district of residence is presented in Figure 3. Thirteen (65%) of the patients pursued agriculture as a profession and 12 (60%) were engaged in animal husbandry. Eight patients (40%) had a recent history of activity in nature (such as picnics, camping) before the onset of symptoms. Nine (45%) had rodents near the house, while 4 (20%) had direct contact with a rodent. There was a recent history of close contact with game animals in 5 patients (25%), tick bites in 3 patients (15%), and swimming in a lake or stream in 4 patients (20%). The drinking water source of 14 patients (70%) was tap water, while 4 patients (20%) consumed spring water, and 2 patients (10%) drank well water. The drinking water of 10 patients (50%) was chlorinated. While there were cases with similar symptoms in the neighborhood/village where 5 patients (25%) lived, only 1 patient (5%) had someone with the same complaints in their household.

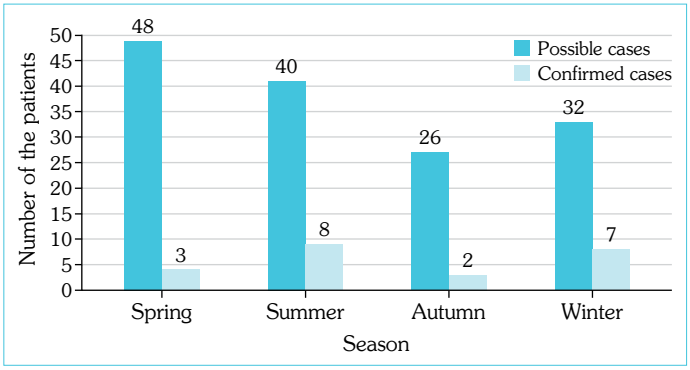

Figure 2. Distribution of tularemia cases according to season

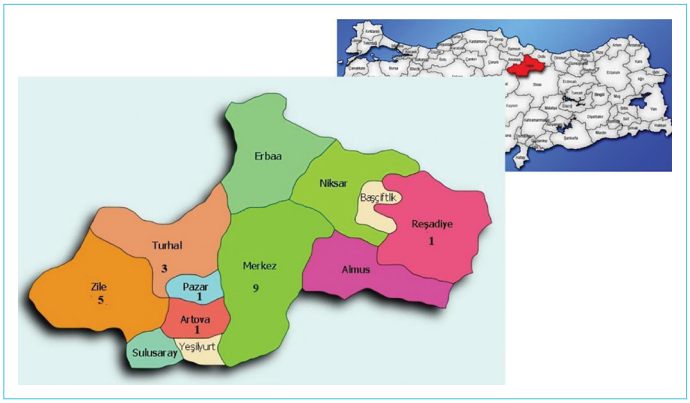

Figure 3. Distribution of tularemia cases according to district of residence

The median length of time between the onset of symptoms and the diagnosis was 30 days (min–max: 7–185 days). The most common symptoms were, in order: lymph node enlargement and/or pain (n=15, 90%), sore throat (n=11, 55%), malaise (n=11, 55%), and fever (n=10, 50%). The most common physical examination findings were, in order: lymphadenopathy (n=18, 90%), fever (n=7, 35%), pharyngitis/tonsillitis (n=6, 30%), and oral mucosal lesions (n=4, 20%). Lymphadenopathy was detected in all patients in neck ultrasonography (USG) or computed tomography (CT) images. Twelve (60%) lymph ganglia were located in the submandibular region, 7 (35%) in jugulodigastric, and 1 (5%) in the posterior cervical triangle. Oropharyngeal tularemia was detected in 15 (75%) patients, glandular in 4 (20%), and typhoidal tularemia in 1 (5%). Leukocytosis (>10.000/mL) was observed in 6 (30%) patients, and an elevated C-reactive protein level (>5 mg/L) in 13 (65%) (Table 1).

Beta-lactam antibiotics for lymphadenopathy were administered to 14 of the patients (70%) before the diagnosis of tularemia, but without benefit. Eleven (55%) patients with confirmed tularemia diagnosis were treated with aminoglycoside monotherapy (9 patients: streptomycin, 2 patients: gentamicin), and 4 (20%) patients received streptomycin + ciprofloxacin, 3 (15%) patients received gentamicin + ciprofloxacin, 1 (5%) patient received streptomycin + doxycycline, and 1 (5%) patient received ciprofloxacin + doxycycline combined therapy. Surgical lymph node drainage was performed in 10 (50%) of the patients, while spontaneous drainage developed in 2 (10%) patients. No case resulted in mortality.

Table 1. Symptoms, physical examination findings, and laboratory findings of tularemia cases

	n	%
Symptoms		
Lymph node enlargement and/or pain	15	90
Sore throat	11	55
Malaise	11	55
Fever	10	50
Anorexia	8	40
Myalgia	6	30
Mouth sores	5	25
Nausea/vomiting	4	20
Rash	4	20
Diarrhea	3	15
Red eye	3	15
Physical examination findings		
Lymphadenopathy	18	90
Fever	7	35
Pharyngitis/tonsillitis	6	30
Oral mucosal lesions	4	20
Laboratory findings		
Leukocytosis (↑>10.000/mL)	6	30
Elevated CRP (>5 mg/L)	13	65

CRP: C-reactive protein

DISCUSSION

The first recorded tularemia epidemic in Tokat Province occurred in December 2005. In a study of that event, tularemia was thought to be transmitted to 8 members of a family through food stores contaminated by mice (10). A review of the literature did not reveal any studies of tularemia in Tokat in the subsequent years. A tularemia epidemic occurred in the neighboring province of Amasya, in the Suluova district, in October 2004, with a total of 86 reported cases. The attack rate was calculated to be 2.3 per 1000. In the Havza district of Samsun Province, also in the Central Black Sea Region, 75 tularemia cases were detected between 2005 and 2007 (11). Two more outbreaks were later noted in Amasya: 28 cases in 2008 and 31 cases in 2009–2011 (12, 13).

Tokat is a province located in the Central Black Sea Region of Türkiye, which includes a large land area in the valleys with suitable vegetation for wild and domestic animals used as hosts by ticks. This area has also been recognized as an epicenter for outbreaks of Crimean Congo hemorrhagic fever, a tick-borne zoonosis (14). Ticks are known to be both vectors and reservoirs in the life cycle of tularemia (15). However, ticks are not at the forefront in the transmission of tularemia in our country; it has been established that transmission mostly occurs through contaminated food and water, though some case series have demonstrated that ticks also cause the transmission of tularemia in Türkiye. Yeşilyurt et al. (16) reported 2 cases of tick-borne tularemia in Yozgat

Province, in the central part of the country. Tularemia after tick contact was also reported in 3 of 22 tularemia cases reported in Düzce Province in the northwest (17). In Kars Province, to the northeast, *F. tularensis* was isolated via a mouse inoculation experiment and it was proven that ticks were vectors for the transmission of tularemia in sheep (18). In the present study, 3 patients had a recent history of a tick bite.

In rural areas, water resources are not regularly chlorinated, and neglected water tanks and village fountains are at risk for tularemia. Tularemia is generally seen in rural areas where animal contact is more common and optimal hygienic conditions are more difficult; the disease is rarely encountered in cities. Independent variables such as consumption of spring water, hunting and eating wild rabbit meat, contact with rodents, unhygienic food consumption, a significant increase in the number of rodents in and around the house, and nature-related activities are among the epidemiological risk factors (6). Tokat has a total population of 597,861 and 33.2% of the people live in villages (19). In our study, 80% of the cases lived in rural areas, 40% had a history of nature-related activities (such as picnics, camping). The drinking water of 50% was not chlorinated and 20% had a recent history of swimming in a lake or stream. In all, 65% were engaged in animal husbandry, 45% had rodents near their house, and 20% had close contact with these animals. Additionally, 25% had a history of contact with game animals and 15% had a history of tick bite.

The oropharyngeal form of tularemia is the most frequently seen clinical form in different regions of the country (5). Engin et al. (20) observed that the oropharyngeal form was the most common (75.9%) in a study conducted in Sivas Province, which is not far from Tokat. Similarly, we also found that the oropharyngeal form was the most common, with a rate of 75%. The second most common type in our study was glandular tularemia (20%). Alkan et al. (21) also reported that glandular tularemia was the second most common form seen after the oropharyngeal type in Samsun Province.

Although the disease may be seen in all seasons, rodent-related infections are more common in the winter months, and tick-related infections are more common in the summer months (6). The epidemic in Tokat reported in 2005 occurred in December (10). In our study, cases were most frequent during the summer and winter months.

In this study, the median length of time between the onset of symptoms and the diagnosis was 30 days. It is noteworthy that the diagnosis period was longer than 3 weeks in previous studies in this country (20, 21). The long delay between the onset of the symptoms and the diagnosis of tularemia may have been due to the fact that they first presented to primary or secondary level health institutions and were given non-specific antibiotics and nonsteroidal anti-inflammatory drugs. Fourteen of our patients (70%) used beta-lactam antibiotics for lymphadenopathy before the diagnosis of tularemia. Since beta-lactam antibiotics are not effective against tularemia, patients whose symptoms did not improve may have subsequently presented at the university hospital. Other reasons for delay in diagnosis could include the physician's failure to think of tularemia because of its rarity, and late patient presentation.

Streptomycin and gentamicin, from the aminoglycoside group, fluoroquinolones, chloramphenicol, and tetracyclines are antibiotics that have proven to be effective against tularemia. Aminoglycosides (gentamicin or streptomycin) should be used in the presence of severe infection (typhoidal and pneumonic tularemia or other forms of long-term and systemic symptoms, development of renal failure, or sepsis). In the treatment of mild or moderate infection, oral fluoroquinolone is recommended as the first choice, and doxycycline as an alternative treatment option. Gentamicin is recommended as first-line therapy in pediatric patients (4). Although monotherapy is often sufficient, some authors recommend combined therapy (22). In our study, 55% of the cases were treated with aminoglycoside, while 45% were treated with combinations of aminoglycoside, ciprofloxacin, and doxycycline.

The most important limitation of our study is the retrospective design. Since it is a rare infection, it is possible that there were other tularemia cases that the clinician did not recognize or test for. Prospective studies are needed to determine the real prevalence in the province and region.

CONCLUSION

This study investigated the prevalence of tularemia over a 10-year period diagnosed at a university hospital in the Central Black Sea Region. Only 20 cases were positive; tularemia is a rare infection in Tokat Province. However, it is possible that there were additional undiagnosed cases. Tularemia should be considered in the differential diagnosis of patients living in rural areas and presenting with fever, cervical lymphadenopathy, or tonsillitis who are unresponsive to beta-lactam agents or in the presence of negative routine cultures.

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Ethics Committee Approval: The Tokat Gaziosmanpaşa University Clinical Research Ethics Committee granted approval for this study (date: 02.09.2021, number: 20-KAEK-189).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – HŞB; Design – ET; Supervision – ET; Resource – ET; Materials – ET, HŞB; Data Collection and/or Processing – HŞB, ET; Analysis and/or Interpretation – HŞB; Literature Search – ET; Writing – ET; Critical Reviews – ET, HŞB.

Conflict of Interest: The authors have no conflict of interest to declare.

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