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Re-emergence of Tularemia in Tokat, Türkiye, After 14 Years: Clinical and Epidemiological Characteristics

Tokat, Türkiye'de 14 Yıl Sonra Yeniden Ortaya Çıkan Tularemi Salgını: Klinik ve Epidemiyolojik Özellikler

Bahadır Orkun ÖZBAY[1](İD), Aliye BAŞTUĞ[2](İD), İsmail KORKMAZ[1](İD), Yasemin HANOĞLU[3](İD), Sibel YAVAŞ[1](İD)

[1] Clinic of Infectious Diseases and Clinical Microbiology, Tokat State Hospital, Tokat, Türkiye
[2] Clinic of Infectious Diseases and Clinical Microbiology, University of Health Sciences Gülhane Faculty of Medicine, Ankara City Hospital, Ankara, Türkiye
[3] Clinic of Medical Biochemistry, Tokat State Hospital, Tokat, Türkiye

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ABSTRACT

Introduction: *The aim of this study was to evaluate the clinical and epidemiological characteristics, treatment options, and outcomes of the tularemia outbreak that began in late 2023 and continued through 2024 in Tokat province, located in the central Black Sea region of Türkiye.*

Materials and Methods: *Patients aged 18 years or older who were diagnosed with tularemia at our center between December 2023 and December 2024 were included in the study. Patient demographic data, clinical characteristics, and antibiotic treatments were obtained from hospital records.*

Results: *According to the Provincial Health Directorate records, 58 tularemia cases were detected in Tokat province between December 2023 and December 2024. Thirty-four of these cases were diagnosed and followed up at our center. The most common clinical form was oropharyngeal tularemia (n= 30, 88.2%). The most common symptom was sore throat (n= 30, 88.2%). The median (min-max) number of days between symptom onset and diagnosis was 26 (6–60). Thirty-three patients (97%) were diagnosed based on a positive microagglutination test. Fifteen of the patients (44.2%) were treated with first-line antibiotics only, and the remaining 19 patients (55.8%) were also given second-line antibiotic treatment after first-line antibiotics.*

Conclusion: *The diagnosis of tularemia should be considered in individuals presenting with compatible clinical symptoms and findings, such as pharyngitis unresponsive to beta-lactam antibiotics or regional lymphadenopathy, particularly in endemic regions. Clinicians in these areas should therefore receive education on this subject. In addition, the use of early diagnostic tests should be expanded in these regions.*

Key Words: *Tularemia; Türkiye; Outbreak; Waterborne diseases*

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ÖZ

Giriş: *Bu çalışmanın amacı, Türkiye'nin Karadeniz bölgesinin merkezinde yer alan Tokat ilinde 2023 yılının sonlarında başlayan ve 2024 yılında da devam eden tularemi salgınının klinik ve epidemiyolojik özelliklerini, tedavi seçeneklerini ve sonuçlarını değerlendirmektir.*

Materyal ve Metod: *Aralık 2023 ile Aralık 2024 tarihleri arasında merkezimizde tularemi tanısı konulan 18 yaş üstü hastalar çalışmaya dahil edilmiştir. Hasta demografik bilgileri, klinik özellikleri ve antibiyotik tedavileri hastane kayıtlarından elde edilmiştir.*

Bulgular: *İl Sağlık Müdürlüğü kayıtlarına göre, Aralık 2023 ile Aralık 2024 tarihleri arasında Tokat ilinde 58 tularemi vakası tespit edilmiştir. Bu vakaların 34'ü merkezimizde teşhis edilmiş ve takip edilmiştir. En sık görülen klinik formu orofaringeal tularemidir (n= 30, %88.2). En sık görülen semptom boğaz ağrısıdır (n= 30, %88.2). Semptomların başlangıcı ile tanı koyulma zamanı arasındaki ortalama (min-maks) gün sayısı 26 (6-60) olarak belirlenmiştir. Hastaların 33 (%97)'ü mikroaglütinasyon testi pozitifliği ile tanı almıştır. Hastaların 15 (%44.2)'i birinci basamak antibiyotiklerle tedavi edilmiş ve geri kalan 19 hastaya (%55.8) birinci basamak antibiyotiklerden sonra ikinci basamak antibiyotik tedavisi de uygulanmıştır.*

Sonuç: *Özellikle endemik bölgelerde, beta-laktam antibiyotiklere yanıt vermeyen farenjit veya bölgesel lenfadenopati gibi uyumlu klinik semptom ve bulgular gösteren bireylerde tularemi tanısı düşünülmelidir. Bu nedenle, bu bölgelerdeki klinisyenler bu konuda eğitim almalıdır. Ayrıca, bu bölgelerde erken tanı testlerinin kullanımı yaygınlaştırılmalıdır.*

Anahtar Kelimeler: *Tularemi; Türkiye; Salgın; Su kaynaklı hastalıklar*

INTRODUCTION

Tularemia is a zoonotic disease caused by *Francisella tularensis* and is seen primarily in the Northern Hemisphere[1]. The disease is transmitted to humans through direct contact of broken skin or mucosal surfaces with the tissues or body fluids of infected animals, arthropod (tick, louse, or fly) bites or stings, consumption of contaminated water or food, or inhalation of infected aerosols[2]. The clinical manifestations of tularemia vary according to the pathogen's route of entry, its virulence, the inoculum size, and the host's immune status. The disease is classified into six main clinical forms according to these factors: oropharyngeal, ulceroglandular, glandular, oculoglandular, typhoidal, and pneumonic tularemia[2,3]. It was first described in Tulare County, California, in 1911[4]. Tularemia was first reported in Türkiye in 1936[3]. Waterborne outbreaks have been described in the Marmara, Central Anatolia, and Black Sea regions[5-7]. In Türkiye, tularemia was included in the list of reportable diseases in 2004. Between 2005 and 2019, 7577 cases were detected in Türkiye. Despite annual fluctuations, the highest number of cases was documented in 2011 (n= 2151)[8]. In 2005, an outbreak affecting seven members of one family was reported in Tokat province[9]. In 2010, 15 cases of oropharyngeal tularemia were detected in Tokat, and this event was considered a waterborne outbreak[10].

In this study, we aimed to evaluate the clinical and epidemiological characteristics and treatment options associated with the tularemia outbreak that re-emerged after 14 years in Tokat province, located in the central Black Sea region of Türkiye. The outbreak began in late 2023 and continued through 2024.

MATERIALS and METHODS

Study Design, Setting, and Ethical Approval

Patients aged 18 years or older who were admitted to the Department of Infectious Diseases and Clinical Microbiology between December 2023, when the first case was identified, and December 2024 and who were diagnosed with tularemia based on compatible clinical findings together with a positive microagglutination test (MAT) or polymerase chain reaction (PCR) result were included in the study. Patients younger than 18 years and those in whom the diagnosis of tularemia could not be confirmed were excluded. The study was approved by the ethics committee of Tokat Gaziosmanpaşa University (approval number: 25-MOBEK-087; date: March 5, 2025). Patient data were obtained retrospectively from the hospital's electronic medical record system.

Microbiological identification and determination of clinical forms

The World Health Organization (WHO) criteria and classification were used to diagnose tularemia

and determine the clinical forms of the cases[11]. All clinical specimens collected from the patients were sent to the Ministry of Health Ankara Public Health Reference Laboratory for analysis. The MAT was performed on serum samples obtained from the patients. PCR was also performed on lymph node aspirate samples. A case was considered positive if the MAT titer was ≥1/160 or if the titer increased fourfold in tests performed at least two weeks apart.

Definition

Treatment failure was defined as the presence of at least one of the following criteria during follow-up despite adequate treatment: persistent or recurrent fever after 72 hours of therapy, ongoing tularemia-related clinical symptoms, lack of a clinical response within two weeks, no reduction in lymph node size, emergence of new lymphadenopathy, development of suppuration or an abscess in involved lymph nodes, or persistent elevation of inflammatory markers such as the leukocyte count, CRP level, and erythrocyte sedimentation rate.

Statistical Analysis

The Statistical Product and Service Solutions (SPSS) statistical package (version 23.0; IBM Corp., Armonk, NY, United States of America) was used for all statistical analyses. Continuous variables that were not normally distributed are presented as medians (minimum–maximum), and categorical variables are presented as numbers and percentages.

RESULTS

After the first case of oropharyngeal tularemia was identified in December 2023, the number of cases peaked in February 2024, and by December 2024, 58 confirmed cases of tularemia had been detected in Tokat province (Figure 1). Thirty-four of these cases were followed at our hospital. All analyses presented in this study were based solely on the 34 patients with tularemia who were diagnosed and followed at our hospital. The median (min-max) age of the patients was 52 years (18–84), and 14 patients (41.2%) were male. In the study, the median (min-max) number of days between symptom onset and diagnosis was 26 (6–60). The most common symptom observed in the patients was sore throat (n= 30, 88.2%). In the vast majority of cases, the clinical form was oropharyngeal tularemia (n= 30). Of the remaining four patients, two had glandular

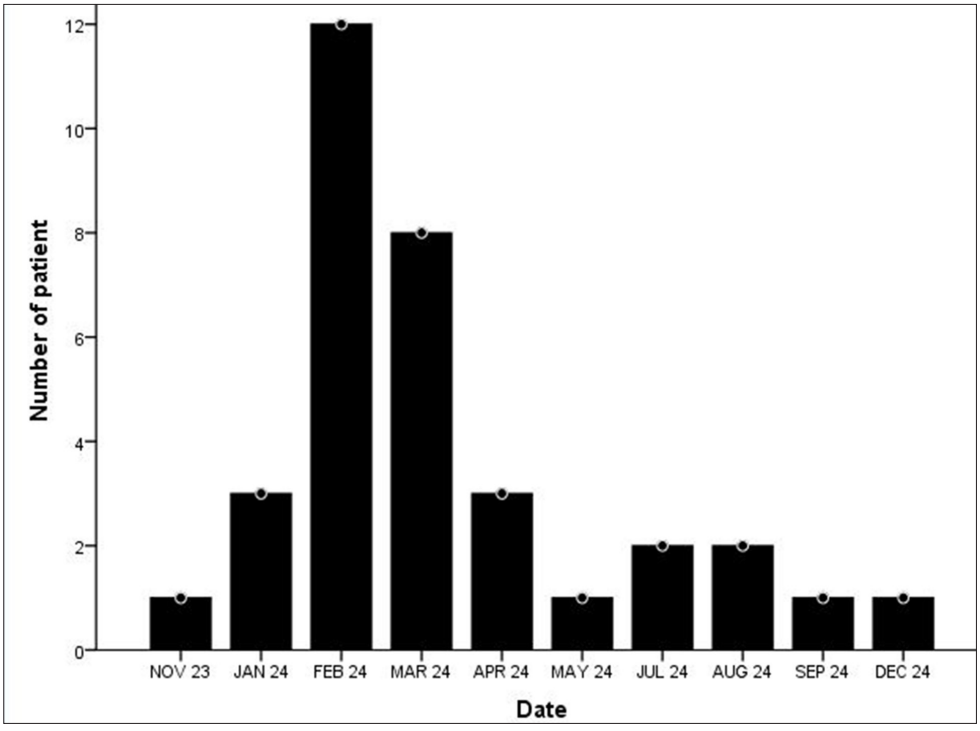


Figure 1. Distribution of tularemia cases by month.

tularemia and two had oculoglandular tularemia. Microbiological confirmation was achieved by a positive microagglutination test (MAT) in 33 patients (97%), whereas one patient (2.9%) was diagnosed by PCR. The median CRP level at the time of admission was elevated. The patients' first-line antibiotic treatments were doxycycline (n= 13, 38.2%), ciprofloxacin (n= 12, 35.3%), and streptomycin (n= 9, 26.5%), in accordance with the WHO guideline. Fifteen of the patients (44.2%) were treated with first-line antibiotics only, and the remaining 19 patients (55.8%) were also given second-line antibiotic treatment after first-line antibiotics. Despite antibiotic treatment, lymph node drainage or excision was required in eight of the patients (23.5%) during follow-up (Table 1).

Table 1. Demographic and clinical characteristics, laboratory parameters, treatments, and outcomes of patients with tularemia

Variable	Tularemia n= 34 (%)
Demographics	
Age, median (min–max)	52 (18–84)
Gender, male	14 (41.2)
Number of days between symptom onset and diagnosis, median (min–max)	26 (6–60)
Symptoms	
Fever	13 (38.2)
Myalgia	10 (29.4)
Fatigue	15 (44.1)
Sore throat	30 (88.2)
Lymph node tenderness	20 (58.8)
Nausea and vomiting	5 (14.7)
Abdominal pain and diarrhea	1 (2.9)
Conjunctivitis	2 (5.9)
Clinical forms of tularemia	
Oropharyngeal	30 (88.2)
Glandular	2 (5.9)
Oculoglandular	2 (5.9)
Lymphadenopathy	
Cervical	25 (73.5)
Submandibular	12 (35.2)
Axillary	2 (5.9)
Periauricular	2 (5.9)
Microbiological diagnosis	
Microagglutination test positivity	33 (97)
Polymerase chain reaction positivity	1 (2.9)
Laboratory parameters, median (min–max)	
Leukocytes, 4.200–10.800/μL	8.695 (5.120–19.380)
Neutrophils, 1.700–7.900/μL	5.265 (1.990–12.310)
Lymphocytes, 1.500–4.500/μL	2.515 (210–6.850)
Monocytes, 100–900/μL	530 (350–1.130)
Basophils, 0–60/μL	20 (0–50)

Table 1. Demographic and clinical characteristics, laboratory parameters, treatments, and outcomes of patients with tularemia (continue)

Variable	Tularemia n= 34 (%)
Eosinophils, 20–520/μL	80 (0–630)
Platelets, 160.000–383.000/μL	304.000 (191.000–501.000)
C-reactive protein, 0–5 mg/L	27.5 (1–116)
First-line antibiotic	
Doxycycline	13 (38.2)
Ciprofloxacin	12 (35.3)
Streptomycin	9 (26.5)
Retreatment (second-line antibiotic)	19 (55.8)
Doxycycline	4 (21)
Ciprofloxacin	7 (36.8)
Streptomycin	5 (26.3)
Gentamicin	3 (15.7)
Lymph node drainage or excision	8 (23.5)
Self-drainage	4 (11.4)
Surgical drainage or excision	4 (11.4)

When the epidemiological histories of the patients were examined, it was determined that 32 of them lived in rural areas and 25 of them were engaged in animal husbandry or animal care. While 20 of the patients used only tap water, 12 used both tap water and spring water. Environmental investigation revealed the presence of *F. tularensis* in spring water and non-chlorinated tap water samples collected from some villages. The organism was isolated by membrane filtration and culture at the Refik Saydam Hygiene Center in Ankara, Türkiye. Eighteen patients reported observing mice, rabbits, or other rodents—either dead or alive—around their homes (Table 2).

Table 2. Epidemiological characteristics of patients with tularemia

Variable	Tularemia n= 34 (%)
Epidemiological characteristics	
Engagement in animal husbandry or animal care	25 (73.5)
Residence in a rural area	32 (94.1)
Engagement in agriculture	20 (58.8)
History of similar disease in the household	4 (11.7)
Similar disease in the neighborhood/village	22 (64.7)
Water sources used	
Only natural spring water	2 (5.9)
Only tap water	20 (58.9)
Both tap and spring water	12 (35.2)
Presence of mice, rabbits, or other rodents (dead or alive) around the house	18 (52.9)
Tick bite	1 (2.9)
Travel history to the outbreak area	1 (2.9)
Outdoor activities (picnicking, hunting, sports, etc.)	1 (2.9)

DISCUSSION

Tularemia is a zoonotic disease that may cause outbreaks. This is particularly evident in the Marmara, Central Anatolia, and Black Sea regions of Türkiye[5-7]. Tularemia cases have been increasing in the Black Sea region since 2004[12]. In this retrospective study, we report 34 cases admitted to our hospital among the 58 cases in an outbreak thought to be waterborne that occurred 14 years after the previous outbreak in Tokat province in the central Black Sea region. Two outbreaks were previously reported in Tokat, in 2005 and 2010[9,10]. An outbreak affecting seven members of one family was first reported in Tokat in 2005. A total of 15 cases of oropharyngeal tularemia were detected in the same location in Tokat in 2010, and the event was considered a waterborne outbreak. The present outbreak affected a larger area (seven districts) and more people (58) than the two previous outbreaks in this province (Figure 2).

The most important finding of our study was the substantial delay between symptom onset and diagnosis despite the occurrence of a tularemia outbreak in an endemic region. The median interval from symptom onset to diagnosis was 26 days (range, 6–60 days), indicating that most patients were diagnosed beyond the critical early treatment period. Early diagnosis is one of the most important determinants of treatment success in tularemia. Previous studies have demonstrated that initiation of appropriate antimicrobial therapy within the first 14 days after symptom onset is associated with significantly better clinical outcomes, whereas delayed treatment markedly increases the risk of treatment failure, prolonged recovery, suppurative lymphadenitis, and the need for surgical intervention. Meric et al. and Ulu Kilic et al. reported that treatment initiated after the first two weeks increased the odds of treatment failure by more than 13-fold [odds ratio (OR)= 13.10, 95% confidence interval (CI)= 5.69–30.15) and was associated with prolonged recovery and progressive lymph node suppuration.[13,14] Therefore, the diagnostic delay observed in our cohort represents not only an epidemiological finding but also a clinically important factor that may adversely affect patient outcomes. Previous studies from

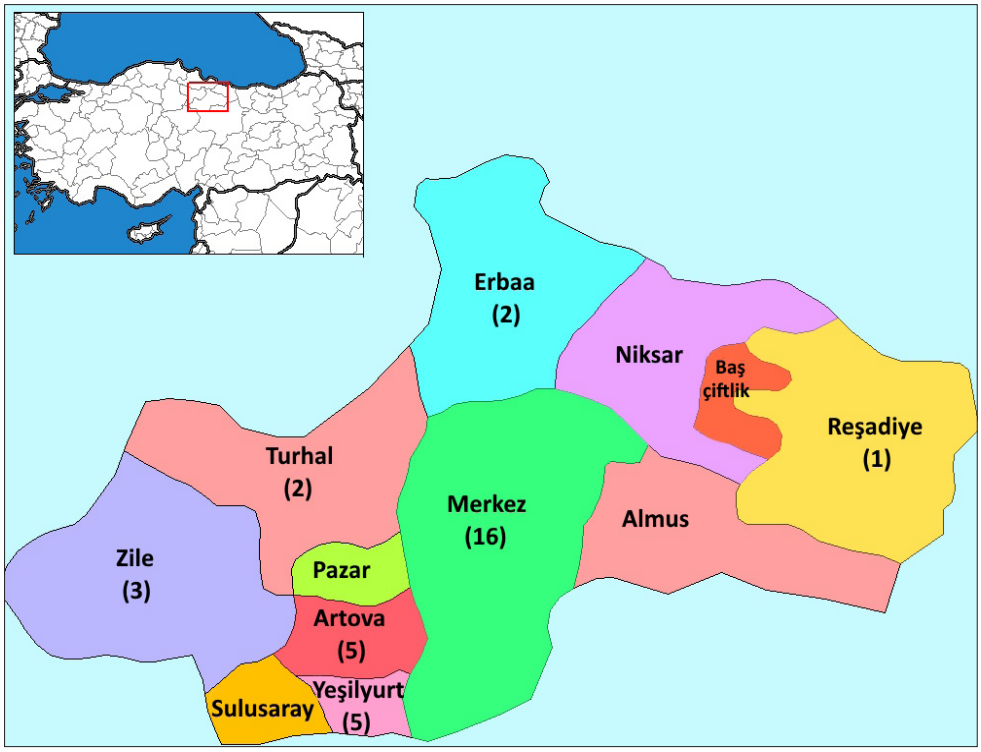


Figure 2. Distribution of tularemia cases by district in Tokat province.

Türkiye have consistently demonstrated a delay in the diagnosis of tularemia. The interval between symptom onset and definitive diagnosis has generally been reported to be several weeks and may extend beyond one month in some patients. In the Düzce outbreak, the mean diagnostic delay was reported as 40.7 ± 22.8 days. Similar delays have been described in other Turkish series, with reported intervals of 19.95 ± 21.81 days in Bursa, 21.6 ± 6.9 days in a military hospital cohort from Ankara, and 53 ± 45.3 days in pediatric patients[15-18]. Furthermore, a nationwide analysis of 7577 tularemia cases reported in Türkiye between 2005 and 2019 showed that only 40% of patients were diagnosed within the first two weeks after symptom onset, indicating that delayed diagnosis remains a substantial challenge in the management of tularemia[8]. One of the primary reasons for this phenomenon may be the nonspecific clinical presentation of tularemia and its broad differential diagnosis. Oropharyngeal tularemia is the most common clinical form of tularemia in Türkiye, and in patients with pharyngitis, clinicians often first consider more common etiologies (*Streptococcus* spp., adenovirus, cytomegalovirus, or Epstein–Barr virus)[8,19]. In areas where the ulceroglandular form is common, the time to diagnosis may be shorter. In a study conducted in Sweden, the median time to diagnosis was reported as seven days[20]. Additionally, the fact that 14 years had passed since the previous outbreak in Tokat province may initially have caused difficulties in diagnosis for clinicians. In patients with epidemiological risk factors, tularemia should be considered in the presence of clinical findings such as pharyngitis unresponsive to beta-lactam antibiotics or regional lymphadenopathy. In regions where tularemia is endemic, educational programs targeting clinicians may improve awareness and facilitate earlier diagnosis, with an emphasis on those working in primary healthcare institutions. It has been documented that the likelihood of complications increases to 20% if treatment is initiated more than two weeks after symptom onset[19]. Serological tests, culture, or PCR tests are used in the diagnosis of tularemia. Serological methods are frequently used in diagnostic procedures. The rise in antibody titers can occur over a period of 2–3 weeks. Culture or PCR testing can be used for early diagnosis[1]. A comparison of PCR testing and culture shows that PCR has higher sensitivity[21].

The distribution of men and women in our study was consistent with the demographic characteristics reported in Turkish studies[8]. The number of female cases was higher than the number of male cases among adults. This may be related to more frequent contact between women and contaminated water during activities such as cleaning, dishwashing, and laundry. The median age of the patients in our study was 52 years. In a study from Sivas province in Türkiye, the mean age of the 205 patients reported in 2024 was 45.9 years[5]. The median age of patients in previous outbreaks in Türkiye was 35 years (2005–2019)[8]. In European studies, the median age has ranged from 40 to 60 years[20,22]. The limited number of patients in this study makes a comprehensive evaluation difficult. The older median age may be attributable to the aging population in rural areas of Türkiye.

A total of 7577 cases were reported in Türkiye between 2005 and 2019, and 53.5% of them had the oropharyngeal form, which is the most common clinical form of tularemia in Türkiye. In our study, oropharyngeal tularemia was detected in 30 patients (88.2%), consistent with national data[8]. In Europe and the United States, the ulceroglandular form is more common than the other clinical forms[20,23]. The clinical form of tularemia observed in a patient depends on the route of transmission. The main route of transmission of tularemia in Türkiye is exposure to contaminated drinking water. The recurrence of the outbreak in Tokat after 14 years may be associated with multiple environmental and ecological factors. Although many patients reported an increase in the number of rodents around their homes and agricultural fields, our study did not include systematic environmental surveillance or objective assessments of rodent populations. Therefore, the potential contribution of increased rodent activity to the re-emergence of tularemia in this region should be interpreted with caution and warrants further investigation through dedicated ecological studies. In addition, similar to other outbreaks reported in the literature,

this outbreak began in winter (December 2023), reached its peak in February, and gradually declined in spring[5,8].

Antibiotics for the patients were selected in accordance with the guidelines established by the WHO[11]. All patients received the appropriate antibiotic for the appropriate duration and at the appropriate dose. Nineteen patients (55.8%) received second-line antibiotic therapy. The rationale for administering treatment again was the presence of persistent lymphadenopathy. The need for retreatment is influenced by two factors: an inappropriate duration or dose of previous treatment and a delay in antibiotic treatment due to delayed diagnosis[1,24]. Because of the small number of patients, no comparison could be made between antibiotics in terms of treatment success. A systematic review of studies published between 1993 and 2023 on the antibiotic treatment of tularemia demonstrated no significant differences in efficacy among various antibiotic agents[23,25]. In pneumonic tularemia only, ciprofloxacin may have a slight advantage over other antibiotics [26].

This study has several limitations. First, because it was conducted at a single center, not all tularemia cases occurring in Tokat province could be included, which may limit the generalizability of the findings and introduce referral bias. Second, the retrospective design may have resulted in incomplete clinical or epidemiological data. Third, the relatively small sample size limits the statistical power of the study. In addition, molecular confirmation by PCR was not available for all patients, particularly during the early phase of the outbreak, potentially leading to underestimation of microbiologically confirmed cases. Finally, environmental investigation data were limited, preventing a comprehensive assessment of the source and transmission dynamics of the outbreak.

CONCLUSION

In this study, we presented a waterborne tularemia outbreak in Tokat province, located in the Black Sea region, in which a larger area and a higher number of patients were reported than in the previous outbreak, which occurred 14 years ago. The diagnosis of tularemia should be considered in individuals presenting with compatible clinical symptoms and findings, such as pharyngitis unresponsive to beta-lactam antibiotics or regional lymphadenopathy, particularly in endemic regions. In our study, the median time to diagnosis was 26 days, highlighting the need for increased clinical awareness and earlier recognition of tularemia to prevent diagnostic delays. Consequently, clinicians in these areas should receive appropriate education. In addition, the use of early diagnostic tests should be expanded in these regions.

ETHICS COMMITTEE APPROVAL

This study was approved by the Tokat Gaziosmanpaşa University Faculty of Medicine Ethics Committee (Decision no: 25-MOBEK-087, Date: 05.03.2025).

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: BOÖ, AB

Analysis/Interpretation: BOÖ, İK

Data Collection or Processing: BHÖ, SY

Writing: BOÖ, YH

Review and Correction: BOÖ, AB, İK

Final Approval: All authors

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Address for Correspondence/Yazışma Adresi

Dr. Bahadır Orkun ÖZBAY

Clinic of Infectious Diseases and Clinical Microbiology,
Tokat State Hospital,
Tokat, Türkiye

E-posta: orkunozbay8@gmail.com