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Original Article

A rare cause requiring consideration in the differential diagnosis of neck masses: tularemia

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Abstract

Introduction: Tularemia is a zoonotic disease caused by the Gram-negative coccobacillus *Francisella tularensis*. It is frequently overlooked in the differential diagnosis of neck masses because of its rarity. The purpose of this study is to report cases diagnosed with tularemia among patients presenting to our clinic with neck masses and to share our experience.

Methodology: Patients presented to our hospital with cervical masses and diagnosed with tularemia were included in this retrospective study. Medical files of all patients were evaluated, and physical examination findings, titration values, date of diagnosis, location of the abscess or mass, place of residence, occupation, drinking water sources, sedimentation (SED), C-reactive protein (CRP), and white blood cell (WBC) values were recorded.

Results: Seventy-six patients were included in the study. Forty patients (52.6%) were living in rural villages and 36 (47.4%) in urban areas. Thirty-one (40.8%) were engaged in animal husbandry and 29 (38.2%) in agriculture. In terms of drinking water sources, 59 patients (73.6%) obtained water from the mains, while 10 (13.32%) used well water. The most frequently observed clinical findings were swelling in the neck, sore throat, lethargy, and fever. Neck swelling frequently occurred in levels II and III.

Conclusions: Since tularemia is rare and there are no specific clinical findings, diagnosis may be problematic. Ear, nose and throat (ENT) specialists should be familiar with the clinical symptoms of tularemia in the head and neck region and should consider a preliminary diagnosis of tularemia in the differential diagnosis of persistent neck masses.

Key words: tularemia; bacterial pathogens; neck mass; cervical swelling.

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Introduction

Neck masses are a clinical condition that cause severe anxiety in patients and can be encountered in almost all age groups [1]. Numerous diseases can be evaluated in the differential diagnosis of neck masses, with congenital, inflammatory, and neoplastic causes requiring particular consideration [2-4]. Tularemia is a zoonotic disease caused by the Gram-negative coccobacillus *Francisella tularensis*. Although tularemia is classically endemic in the northern hemisphere countries such as the US, Russia, Sweden and Norway, it can be encountered all over the world. Tularemia outbreaks have increased in recent decades in non-endemic countries such as Turkey, Kosovo, and Spain [5]. According to the 2019 Annual Epidemiology Report, European Union countries reported 1463 confirmed cases of tularemia with overall notification rate of 0.3 cases per 100,000 population [6]. Despite being one of the inflammatory causes requiring consideration in the differential diagnosis of neck masses, it is frequently overlooked because of its rarity [7,8]. The disease is frequently transmitted to humans by direct contact with infected animals, or by bites from arthropods such as ticks, lice, and flies that carry the agent. Other sources of transmission include the consumption of contaminated water or foods, and inhaling infected aerosols [9]. There are various different forms of tularemia – ulceroglandular, glandular, typhoid, oculoglandular, pulmonary, and oropharyngeal [8]. The ulceroglandular form most frequently results from tick and fly bites and is seen worldwide, while the oropharyngeal form is transmitted by the consumption of contaminated food and water [8,10]. Localized symptoms and findings in the head and neck are found in 11-45% of tularemia patients. However, diagnosis can be problematic for clinicians

due to non-specific symptoms such as fever, pharyngitis, fatigue, and cervical lymphadenopathy [5,11,12]. Persistent cervical masses can mimic malignancy if treatment directed towards the agent is not administered. The most important stage in diagnosis is therefore suspicion of tularemia, and the condition must be considered as a differential diagnosis. In this study, we aimed to report the patients presented to our clinic with neck masses and diagnosed as tularemia and to share our own experience.

Methodology

The study was conducted after obtaining ethical approval from the local ethical committee (approval number 2020:47). Patients presented to Ataturk University Medical Faculty Ear, Nose, and Throat (ENT) Department with cervical masses and diagnosed with tularemia between February 2016 and December 2019 were included in this retrospective study. A detailed physical examination was performed in all patients who presented with the complaint of a neck mass. Fine-needle aspiration, ultrasonography and/or tomography were performed in patients who were diagnosed as having abscesses after the examination. Since tularemia was endemic in our region in the relevant period, samples were taken for tularemia diagnosis from all patients whose abscess diagnosis was confirmed. The patients diagnosed with tularemia were included in this study. The diagnosis of tularemia was based on microagglutination test (MAT) detecting *F. tularensis*-specific antibodies with a threshold value of 1/160 or higher for diagnosis [13]. Patients diagnosed with tularemia and accompanying infectious diseases, autoimmune diseases or malignancies were excluded from the study.

The patients included individuals referred to the ENT clinic from external centers or presenting directly, or patients with cervical masses referred to us from the infectious diseases' clinic. The medical files of all patients were evaluated and physical examination findings, titration values, date of diagnosis, location of the abscess or mass, place of residence, occupation, drinking water sources, and sedimentation (SED), C-reactive protein (CRP) and white blood cell (WBC) values were recorded. In addition, the cervical ultrasonography (USG) and/or computed tomography results were evaluated. The data collected were analyzed using the IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

Table 1. Clinical findings.

Symptoms	Present	Absent
	n (%)	n (%)
Sore throat	41 (46.1)	35 (53.9)
Mouth sore	20 (26.3)	56 (73.7)
Weakness	41 (46.1)	35 (53.9)
Fever	36 (47.7)	40 (52.6)
Cervical swelling	73 (96.1)	3 (3.9)
Eye redness	9 (11.8)	67 (88.2)
Skin ulcer	5 (6.6)	71 (93.4)

Results

76 patients aged 4 to 65 years (mean 28.9 ± 14.5) were included in the study. Sixty-two percent of patients were aged 10-40 years (28% between ages 10-20, 20% between ages 20-30, and 24% between ages 30-40). Forty patients (52.6%) were diagnosed by the physicians in the ENT clinic, while 36 (47.4%) were diagnosed by the physicians in the infectious diseases clinic and then referred to our clinic. Forty-four (57.9%) patients were women and 32 (42.1%) were men.

Forty patients (52.6%) lived in rural villages and 36 (47.4%) in urban areas. Thirty-one (40.8%) were engaged in animal husbandry and 29 (38.2%) in agriculture. In addition, 25 patients were engaged in both animal husbandry and agriculture while 41 patients were working in sectors other than agriculture and animal husbandry.

In terms of drinking water sources, 59 patients (73.6%) obtained water from the mains, while 10 (13.3%) used well water. The remaining 7 patients used bottled water.

The most commonly reported form of tularemia in our region is oropharyngeal tularemia. Almost all the patients hospitalized in our clinic had a history of tonsillopharyngeal infection, particularly sore throat, at the onset of the disease. However, throat symptoms improved by the time of presentation in 41 patients (46.1%). Swelling in the head and neck region and abscess foci were a more common symptom (73 patients, 96.1%). The clinical findings of the patients are summarized in Table 1.

Cervical abscess was detected in 64 patients (84.2%) and multiple abscess formed in 13 (17.1%). The most common abscess locations in patients with single abscesses were the second and third levels, followed by the fourth level. In addition, parapharyngeal abscess was detected in three patients with single abscess and parotid abscess in two patients (Table 2). Cervical abscesses at various levels in the patients presenting with multiple abscesses were accompanied by parapharyngeal abscess in three cases, peritonsillar abscess in one case, and retropharyngeal abscess in one case.

In terms of seasonal distribution, the disease was most frequently seen in winter and fall, and least frequently in summer. Patients' disease course by season are illustrated in Figure 1.

Patients' laboratory characteristics are shown in Table 3. As seen from the table, the CRP and SED values were increased in patients with tularemia while the WBC values were in the normal range. MAT titres were between 1/160-1/1280.

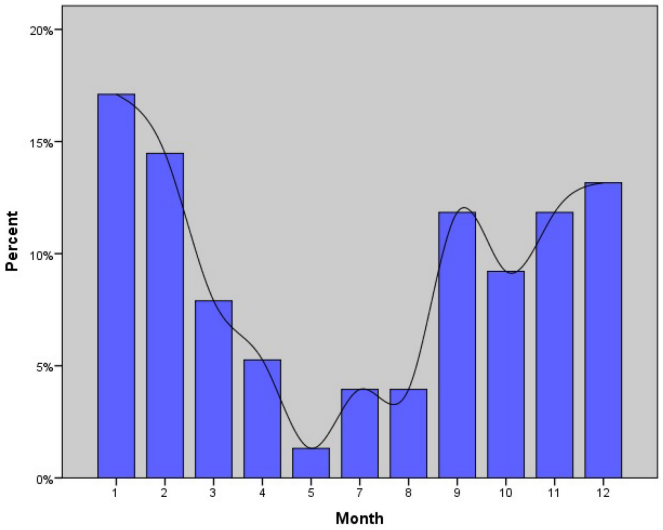
Non-specific findings such as lymph node growth, central necrosis, a heterogeneous appearance, and abscess formation, which can be seen in several infectious diseases, were observed in the imaging of our patients. The computerized tomography scans of four patients with abscesses were presented in Figure 2.

Twelve patients received antibiotherapy alone, with no surgical procedure, while the remaining 64 patients underwent abscess drainage or drainage with biopsy before the antibiotherapy. Patients were started on streptomycin following diagnosis and consultation with the infectious diseases department. Ciprofloxacin was added to treatment in case of late response to treatment or recurrence. 16 patients underwent lymph node biopsies and histopathological examination. Granulomatous inflammation with or without necrosis and suppurative inflammation were reported in biopsy results. No mortality was observed in our patients.

Table 2. Localization of single abscess.

	n = 51 (%)
Level I	6 (11.7)
Level II	19 (37.3)
Level III	12 (23.6)
Level IV	9 (17.7)
Parapharyngeal	3 (5.8)
Parotis	2 (3.9)

Figure 1. The seasonal distribution of tularemia cases.



Discussion

While primary or metastatic tumors, congenital masses, upper airway diseases, dental pathologies, viral lymphadenopathies, cervical lymphadenopathies caused by non-tuberculous mycobacteria, and granulomatous diseases such as tuberculosis are more commonly evaluated in the differential diagnosis of masses in the head and neck, tularemia is less often considered, or diagnosis may be missed, due to its rarity and ability to mimic the clinical manifestations of those diseases [14,15]. Diagnosis of tularemia is problematic due to its exhibition of differing manifestations and rarity, and treatment is therefore generally initiated late.

Tularemia is a zoonotic disease caused by *F. tularensis*. Despite its high virulence, it is not transmitted from human to human. Transmission occurs through swallowing, inhaling or direct contact with infected animals, rodents, lagomorphs, ticks, or other similar vectors. The disease can even emerge through bacterial inoculation in small quantities.

Tularemia is most frequently seen in the northern hemisphere. The incidence is relatively higher in North America and Scandinavian countries than elsewhere. However, tularemia outbreaks have also been reported in countries such as Turkey, Kosovo, Bulgaria, France, Germany, Spain, Poland, Switzerland, and Russia. The most frequent form varies according to the country. In North America and European countries, ulceroglandular tularemia represents 80% of all tularemia cases. While in Turkey, Bulgaria, and Kosovo, oropharyngeal tularemia, which is generally transmitted through contaminated water and foods, is the most frequent form [16-19].

Tularemia has generally assumed greater importance in Turkey in recent years because of

Table 3. Laboratory findings.

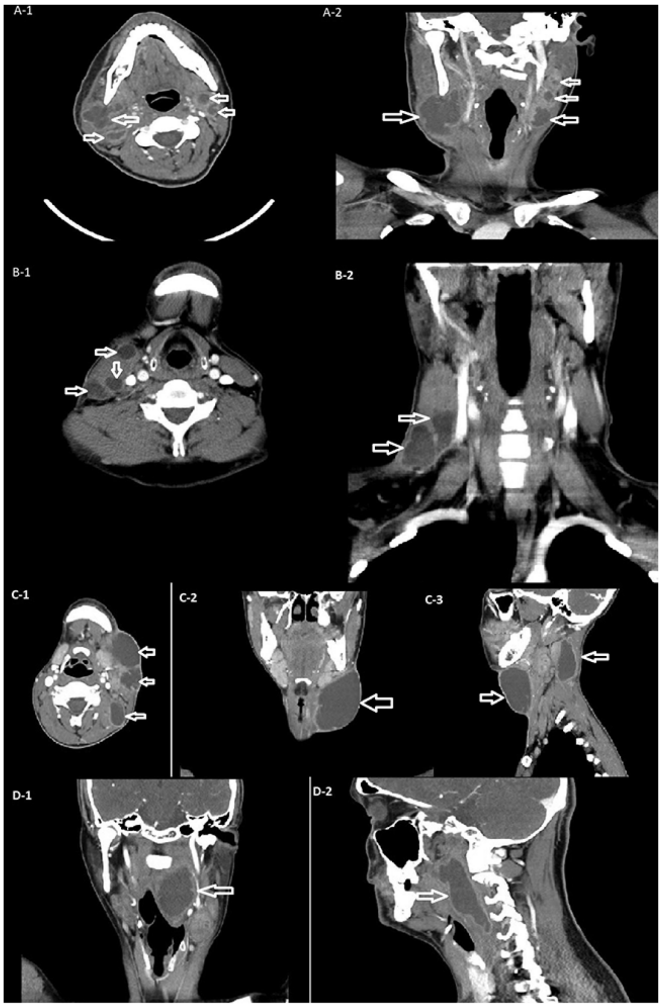
	Min.	Max.	Mean ± SD	Range
Sedimentation	3	104	36.8 ± 21.3	0-20
CRP	3	157	29.6 ± 36.7	0-5
WBC	4	16	9.9 ± 2.6	3.9-10.8
MAT Titres	1/160	1/1280		

SD: Standard deviation; CRP: C-reactive protein; WBC: White blood cell; MAT: Microagglutination test.

outbreaks deriving from water sources [20,21]. Aktas *et al*. reported an outbreak of 55 cases of oropharyngeal tularemia detected in 2013 and derived from drinking water [13]. These outbreaks led to a greater awareness for tularemia when diagnosing masses. Comparative case series were reported by ENT physicians, albeit few in number [14,16,22-24]. In the present study, 22.3% (17 patients) did not use water from the mains, relying instead on spring or well water. In addition, 52.6% (40 patients) lived in rural villages with greater infrastructural problems compared to cities. Moreover, 40.8% (31 patients) were engaged in animal husbandry and 38.2% (29 patients) in agriculture.

It has been reported that tularemia, which is more common in spring and summer in many countries, often occurs in autumn and winter in our country [25]. In studies on the seasonal distribution of the disease; factors such as temperature differences, rain conditions, wind speeds, and migration routes of birds were discussed, but a definite reason could not be identified [26]. The disease, which is mostly transmitted by ticks in Europe, occurs in our country as a result of contact with water contaminated by rodents and drinking this water. Since autumn and winter months are suitable for hunting in our country, contact with rodents increases during these months. This may explain the fact that the disease is seen in our country at different times than in other countries. As a matter of fact, in our study, it was determined that the disease was more common in autumn and winter months.

Figure 2. Axial (A-1) and coronal (A-2) CT images show multiple abscess formation at level II and III. Axial (B-1) and coronal (B-2) CT images show multiple unilateral neck abscess formation. Axial (C-1), coronal (C-2) and sagittal (C-3) CT images show multiple unilateral abscess formation at level II-III and V. Coronal (D-1) and sagittal (D-2) CT images show isolated large parapharyngeal abscess formation. Arrows show the abscesses.



Routine laboratory tests of tularemia patients produce non-specific findings. On the basis of our own experience, while CRP and SED increase significantly, depending on the severity of the clinical course of the disease, no such increase occurs in WBC values, which were within normal limits in many patients. This suggests the possibility of tularemia in patients presenting with infected cervical masses.

The clinical manifestation of oropharyngeal tularemia initially mimics streptococcal tonsillopharyngitis, producing symptoms of tonsillar infection and ulcers with sore throat. No clinical response is obtained to beta-lactam antibiotics, and cervical and parapharyngeal lymphadenopathies possibly with accompanying suppuration and abscess foci may be observed [18,27]. Abscess foci were present in 64 of the 76 patients in the present study, a single focus in 51 patients and multiple foci in 13 patients. Abscesses were most frequently detected in the second and third levels of the neck, followed by the fourth.

The most commonly reported form of tularemia in our region is oropharyngeal tularemia. However, on the basis of our own experience, we think that oropharyngeal symptoms in many patients improve in the time up to their referral to our clinic and assume the appearance of the glandular form in which cervical lymphadenopathies and abscess formations predominate. In support of this idea, although tularemia generally causes outbreaks deriving from water in the summer months, in the four years of the outbreak patients were most frequently referred to our clinic in the fall and winter. We think that patients with oropharyngeal tularemia were misdiagnosed as tonsillopharyngitis at the beginning of the disease. Most of them received beta-lactam antibiotheraphy before presenting to our clinic. After 7-10 days of this

ineffective treatment, patients were referred to our clinic for further investigations. This time led to the development of a form in which suppuration and abscess foci in the head and neck predominated.

Suppurative lymphadenopathy can be detected radiologically by USG of head and neck masses suspected of representing tularemia. However, Computerized Tomography (CT) or magnetic resonance imaging (MRI) can provide more useful information in terms of determining nodal features and the degree of disease [28]. The abscess is observed on ultrasonography as a hypo-anechoic fluid loculation with thick irregular hyperechoic walls. Internal hyperechoic areas may be present depending on the debris content. On CT, it appears as a relatively low central hypodense lesion with an irregular and thick contrast enhancing wall. There were no specific findings indicative of tularemia in USG or CT.

Histopathological examination of a lymph node in tularemia may detect chronic granulomatous formations. Epithelioid histiocytes, lymphocytes, macrophages, and giant cells may also be observed [29]. Similar histopathological features can be observed in other diseases, particularly tuberculosis, cat scratch disease, sarcoidosis, and histoplasmosis.

Extrathoracic tuberculosis essentially involves the cervical lymph nodes, which can result in misdiagnosis with tularemia [30]. Tuberculosis can be falsely diagnosed if tularemia is not considered as a differential diagnosis. Tularemia patients respond to anti-tuberculous therapy including streptomycin. Patients can therefore be exposed to unnecessary side-effects of long-term anti-tuberculous therapy. However, this can be prevented by performing tularemia agglutination tests [14,31]. In a previous study, 96 out of 1,170 patients treated for thoracic tuberculous lymphadenitis were shown to be seropositive for tularemia following serological tests [30].

Serological tests are the most commonly employed technique for diagnosing tularemia. However, serological test results can be negative particularly in the first two weeks of infection [8,32]. Rapid results can be obtained from secretions, exudates, or blood using the polymerase chain reaction (PCR) technique. The materials collected can be sown onto a culture medium containing cysteine, and a diagnosis can be made based on the culture results. Although growth in culture is of considerable value for diagnosis, false negative results can be encountered from culture. Biosafety Level 3 laboratory conditions are also required to protect the staff during such investigations [33,34]. For this reason, all of these tests are performed in a single center in our country. In our study, all samples were sent to this center for analyses. Since this center uses MAT as the diagnostic test, PCR and culture results are not available in our study. Enzyme-linked immunosorbent assay or agglutination methods are employed in serological tests. Titers between 1/10 and 1/80 indicate that patients do not have tularemia. A titer exceeding 1/160 at tube agglutination, greater than 1/128 at microagglutination, or a four-fold increase in two to four weeks are diagnostic for tularemia. Since test results can be negative in the first 10-14 days of the onset of the disease, serological tests must be performed later [33].

In their multi-center study and review of the literature, Tuncer *et al.* reported that fine needle aspiration cytology could provide useful information for early diagnosis. However, this information is insufficient for the diagnosis of tularemia. Fine needle aspiration can provide rapid material for PCR and culture studies. The authors also reported the need for confirmation of diagnosis with serological studies [35].

Streptomycin is the first-choice drug in the treatment of tularemia. Gentamicin, tetracycline, quinolones, and chloramphenicol are also effective. Beta-lactam antibiotics, macrolides, and lincosamides that are frequently prescribed for upper airway infections are not effective treatment and can result in delayed diagnosis and chronicity of the disease [14,36,37]. Two grams of intramuscular streptomycin over 10 days is effective as a first-choice therapy in adult patients. It is also effective in children at 15 mg/kg/day over the same period. The therapeutic period may sometimes exceed two weeks in patients with slow clinical improvement [21,38].

Previous publications have shown that ciprofloxacin is effective in both adult and pediatric tularemia cases [39,40]. On the basis of our own experience, ciprofloxacin in addition to streptomycin provides more effective results than other antibiotics in cases that fail to exhibit the desired response to streptomycin therapy. Although there are no studies showing this effectiveness in the literature, further studies can be done on this subject. Ciprofloxacin was administered at a dosage of 2 x 500 mg/day in adult cases, and 15 mg/kg/day divided into two doses at 12-h intervals in pediatric cases. Appropriate antibiotherapy, together with drainage in the presence of abscess formation, is essential. Surgical drainage is imperative in cases of large and recurring abscesses, while needle aspiration may be sufficient for small and superficial abscesses. Suppuration and abscesses may be seen in the lymph nodes even with appropriate antibiotherapy

in patients with lymphadenopathy receiving late treatment. The abscess should be drained, while treatment is maintained. Mortality due to bacteremia may occur if these are left untreated. One broad-based study from the USA in 1964-2004 described tularemia as a potentially fatal disease with mortality rates between 1% and 14% [41].

There are a number of limitations in the present study. PCR was not performed for diagnosis, and due to the high risk of transmission, culture growth, the gold standard for diagnosis, was also not performed. As mentioned earlier, biosafety level 3 laboratory conditions are required for performing tularemia tests. All tests in our study were performed in laboratories of the Ministry of Health and results were obtained from the Ministry of Health system. The Ministry uses MATs as the diagnostic test, so PCR and culture results could not be performed.

Conclusions

Tularemia must be considered in the differential diagnosis of patients with histories of tonsillopharyngitis or cervical lymphadenopathies that do not respond to previous antibiotheraphy. Symptoms may partially improve with other antibiotherapies even when the condition is not diagnosed, and definite diagnosis thus becomes more difficult. Suppurative infection and abscesses may develop in the lymph nodes and neck spaces requiring surgical intervention if specific treatment is delayed. Early diagnosis is therefore of considerable importance. There are no specific signs or symptoms to distinguish tularemia from other types of abscesses. Since the diagnosis is made only by suspicion, ENT specialists should be familiar with the clinical symptoms of tularemia in the head and neck region and should consider a preliminary diagnosis of tularemia in the differential diagnosis of persistent neck masses especially when resistant to treatment.

Authors' Contribution

MSS, KK, BA, FKC, HA and AS designed the study. HA and FKC collected the data. Data were analyzed by MSS, KK, BA and AS. Statistical analyses were performed by KK. The manuscript was written by MSS and KK. All the authors read and approved the final manuscript.

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