

Clinical manifestations of 16 oropharyngeal tularemia patients: experience of a referral hospital in the city of Konya, Turkey

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Aim: In recent years, tularemia's importance has been reemerging in Turkey. However, the majority of tularemia cases were reported in the northern cities of Turkey. In this study, we report 16 oropharyngeal tularemia patients living in rural areas of the city of Konya, which is located in the southern zone of the Central Anatolia Region of Turkey.

Materials and methods: Sixteen patients (12 males, 4 females; mean age: 33.7 years, range: 10–73 years) were included in this study. All patients were admitted to our clinic for the evaluation of intractable cervical mass lesions. The diagnosis of tularemia was made after exclusion of other possible causes of the neck masses and the presence of a positive tularemia agglutination test. Each patient was treated with streptomycin and doxycycline for at least 3 weeks.

Results: All patients suffered oropharyngeal stiffness. There were neck mass and tonsillitis on the same side in 2 patients, neck mass and acute pharyngitis in 3 patients, and only swelling in the neck region in 11 patients. One of the patients with tonsillitis had common maculopapular skin rashes with fever. Thirteen patients had mass at level 2 zones, 11 patients had mass on the right side of the neck, and 5 patients had mass on the left side of the neck. The right parotid gland was involved in 1 patient. Nine patients were successfully treated with only antimicrobial agents. Lymph node excision was performed in 6 patients, and parotidectomy was performed in 1 patient.

Conclusion: This is the second series of tularemia from the city of Konya in Turkey. Tularemia should be considered in the differential diagnosis of patients with intractable neck mass, because early diagnosis and treatment may prevent surgical interventions.

Key words: Tularemia, neck mass, surgery

1. Introduction

Tularemia is a zoonotic disease caused by *Francisella tularensis*, which is a pathogen of mainly gnawing animals (1,2). It was first identified in the city of Tulare, CA, USA, approximately 100 years ago. Although tularemia outbreaks have been reported in many parts of the northern hemisphere, it was generally regarded as a rare disease in most other areas. Depending on the route of microbial transmission, different clinical forms of tularemia can be seen, including ulceroglandular, glandular, pneumonic, oropharyngeal, oculoglandular, and systemic (typhoidal) forms. Tularemia is transmitted mainly by insect bites, contact with infected animals, or consumption of contaminated animal products and/or water.

The first tularemia outbreak was reported in Turkey in 1936 (4). However, in recent years, an increasing number of tularemia cases have been reported in different regions of Turkey, and it has become a reemerging situation (5,6). The majority of tularemia cases were reported in the northern

cities of Turkey, including Samsun, Kocaeli, Sakarya, Tokat, Edirne, and Bursa (2,3,7–10). In Turkey, waterborne outbreaks are responsible for many cases. Accordingly, the oropharyngeal form is more common in Turkey (2,6,7,11–13). In the oropharyngeal form, intractable mass lesions in the cervical region are a frequent finding (3,7,14), which makes tularemia an important differential diagnosis for such lesions in recent years.

To our knowledge, only 3 studies were reported from Central Anatolia. However, those studies were reported from university hospitals, which were tertiary reference centers for Central Anatolia. In one of those studies, the authors wrote that the patients were from Çorum, which is located in the northern zone of Central Anatolia (6). In the second study, the authors reported that the patients were living in the Central Anatolia Region of Turkey without specifying the exact origin of the patients (5). In this study, we report the clinical features, management strategies, and outcomes of 16 oropharyngeal tularemia patients

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who were admitted to a single otorhinolaryngology clinic for the evaluation of intractable cervical mass lesions. All patients were living in rural areas of the city of Konya, which is located in the southern zone of the Central Anatolia Region of Turkey. To the best of our knowledge, this is the second study on tularemia cases in the city of Konya.

2. Materials and methods

This study was performed in the Otorhinolaryngology Clinic of the Ministry of Health Konya Training and Research Hospital. Sixteen patients (12 males, 4 females) who were admitted to our clinic with the complaint of swelling in the neck region between 2010 and 2012 were included in this study. The mean age of the patients was 33.7 years (range: 10–73). Mean duration of symptoms before admission to our clinic was 3–4 weeks (range: 1–8). Each patient was evaluated with an ear, nose, throat, head, and neck examination, followed by an endoscopic examination. Complete blood cell count, erythrocyte sedimentation rate, C reactive protein levels, and serological tests for human immunodeficiency virus, Epstein–Barr virus, cytomegalovirus, *Toxoplasma*, and *Brucella* were also performed. Chest radiography, tuberculin skin test, acid-fast staining, and tuberculosis culture of sputum were done. The neck mass of each patient was evaluated by ultrasonography, magnetic resonance imaging, and/or computerized tomography of the neck. Serum samples from each patient for the serological evaluation of tularemia were sent to the Refik Saydam Public Hygiene Center, which is a reference laboratory for the evaluation of infectious diseases, including tularemia, in Turkey. The diagnosis of tularemia was made after exclusion of other possible causes of the neck masses, including tuberculosis and malignancy, and the presence of a positive tularemia agglutination test. Antibody titers of $\geq 1:160$ were accepted as positive for the disease. According to the recommendations of the Department of Infectious Diseases, each patient was treated with intramuscular streptomycin (1 g, twice daily) and doxycycline (100 mg, twice daily) for at least 3 weeks. The dose of streptomycin was calculated as 2×15 mg/kg for pediatric patients.

3. Results

All patients were admitted with the complaint of an intractable cervical mass. All had previously been treated with oral and/or a penicillin/cephalosporin group of antibiotics in different medical centers. All of the patients applied in spring and summer months (May–August). None of the patients had a history of hunting or contact with wild animals. Only 2 of the patients were from the same family. All of them were living in rural areas of the city of Konya.

The ear, nose, throat, and head and neck examinations revealed a mass and tonsillitis on the same side in 2 patients, a neck mass and acute pharyngitis in 3 patients, and only swelling in the neck region in 11 patients. One of the patients with tonsillitis had common maculopapular skin rashes with a fever (Table). All patients suffered from an oropharyngeal mass (Figure). Thirteen patients had a mass at level 2 zones, 11 patients had mass on the right side of the neck, and 5 patients had mass on the left side of the neck. The right parotid gland was involved in 1 patient (Table).

Patients' laboratory findings were checked during initial admissions and followed during the hospitalization periods. The mean white blood cell (WBC) count was $11,800/\text{mm}^3$ (8300 – $17,500/\text{mm}^3$). Ten patients had a WBC count of more than $10,000/\text{mm}^3$. The mean erythrocyte sedimentation rate was 81 mm/h (72–117 mm/h). A serological test for tularemia was positive in all patients. The levels ranged from 1/320 to 1/1280. Although the antibody titers were $<1:160$ in the first samplings in 3 patients, the antibody titers were 1/640 in repeated serum samplings (Table).

Cultures of the aspirated materials and the materials drained from the lesions of 10 patients showed no growing microorganisms.

Nine patients were successfully treated with only antimicrobial agents. At the end of 1 month of medical treatment, fluctuation in the lymph nodes was detected in 7 patients. Lymph nodes of those patients were excised in order to prevent fistulization and scar formation. Additionally, parotidectomy was performed in 1 patient. No complications were noted. Neither septicemia nor mortality was observed. At the end of at least a 6-month follow-up period, all patients were completely symptom-free.



Figure. Mass in the neck region.

Table. Clinical and laboratory findings and outcomes of patients.

Patient no.	Sex	Age	Symptom duration (weeks)	Physical examination	ESR	Retention areas	MAT titer	Cured with antibiotic only
1	M	18	2	Neck mass, pharyngitis	74	Upper jugular	1/640	Yes
2	M	25	3	Neck mass	72	Submandibular region	1/640	Yes
3	M	25	4	Neck mass	71		1/640	No
4	F	19	2	Neck mass, tonsillitis, fever, parotid gland involvement	89	Upper jugular, parotid	1/640	Yes
5	M	40	1	Neck mass, pharyngitis, fever	90	Upper jugular	1/1280	Yes
6	M	23	4	Neck mass	77	Upper jugular	1/1280	No
7	F	65	8	Neck mass	72	Upper jugular	1/1280	No
8	M	16	2	Neck mass, pharyngitis	84	Upper jugular	1/1280	Yes
9	M	33	3	Neck mass	82	Upper jugular	1/320	Yes
10	M	16	4	Neck mass	73	Submandibular region	1/1280	No
11	F	64	6	Neck mass	117	Upper jugular	1/1280	No
12	M	46	5	Neck mass	74	Upper jugular	1/320	No
13	F	42	3	Neck mass	84	Upper jugular	1/640	Yes
14	M	24	1	Neck mass, tonsillitis, skin rashes, fever	74	Upper jugular	1/640	Yes
15	M	10	2	Neck mass	81	Upper jugular	1/320	Yes
16	M	73	4	Neck mass	82	Upper jugular	1/320	No

Abbreviations: ESR, erythrocyte sedimentation rate; MAT, microagglutination test.
Symptom duration: time before admission to hospital.

4. Discussion

In this study, we represented clinical data, management strategies, and outcomes of 16 patients who were living in rural areas of the city of Konya in the Central Anatolia Region of Turkey.

Differential diagnosis is of great importance for patients who apply to ear, nose, and throat clinics with complaints of a neck mass. Upper respiratory infections, congenital diseases, tuberculosis, primary neoplasms, and metastasis are generally considered first, and tularemia is overlooked if there are no epidemiological data (12). In general practice, patients presenting symptoms of tonsillitis/pharyngitis and presence of a cervical mass are first generally treated with beta-lactam antibiotics. However, *F. tularensis* releases beta-lactamase and is resistant to those

antimicrobial drugs (8). Likewise, all patients in our study were referred to our center for the evaluation of intractable neck mass after unsuccessful attempts of treatment with beta-lactam antibiotics.

The diagnosis of tularemia may be difficult because the results of routine laboratory tests and the radiological features are nonspecific, such as increased WBC count and acute phase reactants (15–17). *F. tularensis* is a microorganism that grows poorly in standard culture media. In our study, none of the cultures from 10 patients demonstrated any growing microorganisms. Serological tests aid the diagnosis of tularemia in the majority of cases (2,18). Since the bacteria have a single antigenic type, diagnosis through agglutination, microagglutination, and enzyme-linked immunosorbent assay testing is possible.

The serological positivity occurs during the first or second week of disease in agglutination tests. Titers of $\geq 1:160$ are accepted as significant in agglutination tests and $\geq 1:128$ is accepted as significant in microagglutination tests. Additionally, a diagnosis can be made specifically by polymerase chain reaction (3,18). The diagnoses of our patients were made with the demonstration of a positive tularemia agglutination test. However, the agglutination test results were negative in the first samplings in 3 patients in our study, but the antibody titers of those 3 patients were 1/640 in repeated serum samplings (Table). Hence, the agglutination test should be repeated in suspected cases.

It is not completely clear how our patients were infected. Previous data suggest that tularemia is mainly transmitted through unmonitored spring water and consumption of contaminated food in Turkey (2,3,18). Tularemia outbreaks due to contaminated water usually occur in fall and winter, whereas transmission via consumption of hunted animals is more common in summer (1). Our cases can be regarded as sporadic, because only 2 patients were from the same family. There was no history of hunting, contact with wild animals, or animal bites among our patients. Hence, although all of the patients were infected in the spring and summer months (May–August), the most likely means of transmission in our patients was via consumption of unmonitored spring water.

The most common symptoms in tularemia are neck masses, sore throat, and fever (5,6). Other prominent symptoms may include cough, myalgia, chest discomfort, vomiting, sore throat, abdominal pain, and diarrhea, but no clinical signs develop in nearly half of the infected persons (5). In our series, although all patients had neck masses and oropharyngeal stiffness, only 3 patients had the complaint of fever and accompanying sore throat. We think that the reason for this low frequency of those symptoms among our patients is late referral to our clinic.

The most common site of involvement in the neck is the upper jugular node group (5,9). Similar findings were observed in our series (13 patients, 81%). All of our patients had unilateral involvement. Likewise, unilateral involvement was also reported in a majority of the cases in the literature (9,19). Interestingly, 1 of our patients had involvement of the right parotid gland, which has not been reported before.

The first choice of antibiotics is streptomycin. Gentamicin, tetracyclines, and ciprofloxacin are the

alternative agents (10). Antimicrobial therapy should be continued for at least 10–14 days according to World Health Organization guidelines (20). However, the duration of the treatment could be adapted according to the clinical course (21–23). We treated our patients for at least 3 weeks. Early treatment with antimicrobial agents is more effective and can prevent surgical interventions. However, surgical interventions may be necessary in the case of the persistence of cervical lymph nodes or in the case of abscess formation, because wide scars may develop when lymph nodes are drained spontaneously (7). In our series, 9 patients (56%) were successfully treated only with antibiotics. However, lymph node excision was performed in 7 patients, because fluctuation in the lymph nodes was present at the end of 1 month of medical treatment, in order to achieve better cosmetic appearance. In a study by Kızıl et al. (6), 6 patients underwent incision and drainage procedures, 5 patients underwent superselective neck dissection, and 8 patients had only medical treatment. It was seen that better tissue healing with less scarring could be achieved in all patients who underwent superselective neck dissection. Additionally, parotidectomy was performed in 1 patient. On the other hand, the need for surgical intervention was quite variable in the literature, ranging between 34% and 75% in different reports (5,6,10,24). The difference between those series is probably the variation between timing of diagnosis and treatment. In our series, all the patients that medical therapy start within 3 weeks recovered without surgical interventions (Table).

Reported case series from the Central Anatolia Region for oropharyngeal tularemia are limited. In the literature, there are 3 case series for oropharyngeal tularemia from Ankara Province. There is 1 case series from Kayseri and Çankırı provinces (11,25,26). There is 1 case series from Konya (27).

In summary, we herein reported the second series of oropharyngeal tularemia from the city of Konya in the Central Anatolia Region of Turkey. The clinical findings of our patients were generally comparable to those previously reported from Turkey. We could treat more than half of our patients without surgical intervention. Interestingly, medical therapy started within 3 weeks was successful in all patients in our series. Hence, tularemia should be considered in the differential diagnosis of patients with neck mass in order to prevent diagnostic delay and unnecessary surgical interventions.

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