

# Factors Affecting Cervical Lymph Node Suppuration in Oropharyngeal Tularemia Cases

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## ABSTRACT

**Objective:** To determine the factors associated with cervical lymph node suppuration in oropharyngeal tularemia.

**Study Design:** Observational study.

**Place and Duration of Study:** Departments of Infectious Diseases and Clinical Microbiology, Faculties of Medicine, Duzce University and Bolu Abant Izzet Baysal University Turkey, between January 2016 and August 2019.

**Methodology:** Tularemia was diagnosed in clinically compatible cases by micro-agglutination test ( $\geq 1/160$  titres). Positive cases were divided into two groups according to development of suppurated and discharging lymph nodes. If the cases did not develop suppuration and discharge lymph nodes, they were defined as completely healed. If they did, they were defined as "suppurated and drained lymph node group." Demographic and clinical characteristics and acute phase reactants of these groups were compared as to investigate any significant difference between the groups.

**Results:** There were 88 tularemia cases in the current study. Of these, 60 cases were completely healed (68.2%) and 28 cases had suppurated and drained lymph nodes (31.8%). Tonsillopharyngitis was found significantly lower in suppurated and drained lymph node group compared to the completely healed group ( $p=0.016$ ). However, late presentation ( $>14$  days) was found significantly more frequent in suppurated and drained lymph node group compared to the completely healed group ( $p=0.033$ ).

**Conclusion:** In order to prevent suppurative lymphadenitis in oropharyngeal tularemia, it is advisable to start appropriate antimicrobials within 14 days after the appearance of symptoms.

**Key Words:** Oropharyngeal tularemia, Cervical lymph node suppuration, Antibiotic initiation time.

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## INTRODUCTION

Tularemia is an acute, febrile, granulomatous zoonotic disease caused by *Francisella tularensis*, which is a gram-negative intracellular bacterium. The disease is endemic in many parts of the world, particularly in North America, Europe, and Asia. *F. tularensis* is a bacterium that is highly resistant to environmental conditions. Bacteria are transmitted to humans through dermal, oral, conjunctival, or respiratory routes via direct contact with infected animals, contaminated food or water intake, inhalation of contaminated aerosols, or arthropod bites.<sup>1</sup> Depending on the bacterial subtype and the site of entry, the disease is observed in six different clinical forms: ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, and typhoid (septicemic) tularemia. The most common form in North America is ulceroglandular tularemia.<sup>2</sup>

However, the most common form in the European countries is the oropharyngeal tularemia (90%), which is acquired by contaminated water and food and may be the cause of waterborne outbreaks.<sup>3,4</sup>

Clinical symptoms of oropharyngeal tularemia are sore throat, mouth ulcer, tonsillitis, and enlarged lymph nodes in the neck.<sup>5</sup> Early symptoms can be confused with several diseases such as streptococcal tonsillitis, tuberculous lymphadenitis, infectious mononucleosis, and lymphoma. This situation may lead to a delay in the diagnosis.<sup>6</sup> Delay in the use of the appropriate antimicrobials may result in treatment failure and complications.<sup>6-8</sup> Lymph node suppuration is the most common complication.<sup>9</sup>

The aim of this study was to investigate the factors associated with cervical lymph node suppuration in oropharyngeal tularemia.

## METHODOLOGY

After obtaining permission from the local Ethics Committee, the authors retrospectively analysed the medical records of tularemia cases followed up in two medical centres, Faculties of Medicine, Duzce University and Bolu Abant Izzet Baysal University Turkey, between January 2016 and August 2019.

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**Table I: Clinical and laboratory data of the study groups**

	Completely healed group (n=60)	Suppurated and drained lymph node group (n=28)	p-value
Gender, n (%)			
Male	25 (41.7)	16 (57.1)	0.177
Female	35 (58.3)	12 (42.9)	
Comorbidity, n (%)			
Present	31 (51.7)	12 (42.9)	0.443
Absent	29 (48.3)	16 (57.1)	
Hospital admission time, n (%)			
Early ( $\leq 14$ days)	34 (56.7)	9 (32.1)	0.033
Late ( $> 14$ days)	26 (43.3)	19 (67.9)	
Age (years)	53.5 $\pm$ 17.16	48.87 $\pm$ 16.07	0.221
Fever	29 (48.3)	9 (32.1)	0.156
Sore throat	38 (63.3)	13 (46.4)	0.137
Neck swelling	56 (93.3)	28 (100)	0.302
Tonsillit/pharyngitis	40 (66.7)	11 (39.3)	0.016
Conjunctivitis	5 (8.3)	3 (10.7)	0.706
Rash	7 (11.7)	3 (10.7)	>0.999
WBC	8.93 $\pm$ 2.78	9.62 $\pm$ 2.67	0.279
CRP	3.3 (1.03-5.58)	4.15 (1.11-16)	0.307
Erythrocyte sedimentation rate	42 (28.5-71)	69 (36.75-80)	0.077

Patients diagnosed with tularemia were included in the study. All patients were required to have a medical history compatible with tularemia (patients with fever, pharyngitis and cervical lymphadenitis who did not response to beta lactam antibiotics), positive tularemia micro-agglutination test (MA titer  $\geq 160$ ), and first MA test  $< 160$ , but repeat MA test  $\geq 160$  (obtained at least two weeks later).

Pediatric patients (age  $< 18$  years) were excluded. Tularemia MA test was performed in the National Tularemia Reference Laboratory, Public Health Institution.

Tularemia cases were divided into two groups according to development of suppurated and drained lymph nodes. If the cases did not develop suppuration and discharging lymph nodes, they were defined as completely healed group. If they did develop this, they were defined as suppurated and drained lymph node group. Demographic and clinical characteristics such as age, gender, comorbidity, hospital admission time, fever, sore throat, neck swelling, tonsillopharyngitis and conjunctivitis together with acute phase reactants (white blood cell,

c-reactive protein and erythrocyte sedimentation rate) of these groups were compared in order to investigate whether there was a difference between the groups or not. Tonsillitis was defined as tonsillar erythema, hypertrophy or exudate; whereas, pharyngitis was defined as pharyngeal erythema on physical examination. Tonsillopharyngitis referred to both tonsillitis and pharyngitis.

For statistical analysis, Med Calc statistical software 19.0.7 demo version (Med Calc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2019) was used. Homogenously distributed variables were expressed as mean  $\pm$  standard deviation and compared with independent samples t-test. Non-homogenously distributed variables were expressed as

median (inter quartile range) and compared with Mann-Whitney U-test. Categorical variables were expressed as numbers and percentages while compared with the Chi-square/Fisher's Exact test. A p-value  $< 0.05$  was considered as statistically significant.

## RESULTS

There were 88 cases of tularemia in the current study period. Of these cases, 41 (46.6%) were males and 47 (53.4%) were females. The mean age of the patients was 50.34  $\pm$  16.46 years. There were 60 cases (68.2%) in the completely healed, and 28 cases (31.8%) in suppurated and drained lymph node group. There was no statistically significant difference between the groups with respect to age, gender and comorbidity. Hypertension was found in 18 patients, diabetes mellitus in 12, coronary artery disease in nine, hyperlipidemia in eight, thyroid function disorder in seven, chronic obstructive lung disease and skin disease in five each, cerebrovascular event and malignancy in four each, and nephrolithiasis in one patient. Clinical and laboratory data of the study groups are summarised in Table I.

Hospital admission time and tonsillopharyngitis were found statistically different between the groups. Tonsillopharyngitis was found significantly less frequent in suppurated and drained lymph node group compared to the completely healed group (p= 0.016). However, late presentation ( $> 14$  days) was found significantly more in the suppurated and drained lymph node group compared to the completely healed group (p = 0.033).

## DISCUSSION

Oropharyngeal tularemia is characterised by swelling, redness, granulomatous, and suppurative lesions in the affected lymph nodes.<sup>10</sup> Before the appearance of lymph

node symptoms, nonspecific complaints such as sore throat, fever, and weakness cause confusion and delay in the diagnosis of the disease.<sup>11</sup> Delay in diagnosis and effective treatment due to various reasons can lead to enlargement of lymph nodes and abscess formation. Lymph node suppuration was observed in approximately 40% of the cases in the outbreaks.<sup>5,9</sup> In the present study, lymph node suppuration was found in one-third of the cases, which was consistent with previous findings.

Tularemia was found to be more common in males in some studies; however, it was found 1.18 times more common in females in other studies.<sup>12,13</sup> This may be because females are working around contaminated water and food storage places in rural areas and getting more contact with animal feces compared to males. In the present study, tularemia was more common in females, which was consistent with the local previous literature. One study, reported that 63.8% of the patients were older than 30 years.<sup>13</sup> When compared with the literature, the mean age of the patients was higher ( $50.34 \pm 16.46$ ) in the present study. This could be due to the exclusion of pediatric patients in the study group. The effect of age and gender on lymph node suppuration was also evaluated and no statistically significant differences were observed in suppurated and non-suppurated patient groups with respect to age and gender. Conversely, a previous study by Tezer *et al.* reported that female gender is a risk factor for treatment failure.<sup>14</sup>

Previous studies reported significant delay in the diagnosis of tularemia because of low disease awareness.<sup>11</sup> In a study conducted in Turkey, the mean interval between the onset of symptoms and hospital admission was reported as 28.1 days (4-90 days).<sup>9</sup> In other studies, the average hospital admission time reported as 51 days, 40.7 days, and 8 weeks, respectively.<sup>15-17</sup> According to the literature, as the time until admission to hospital increases in oropharyngeal tularemia patients, the risk of complications also increases. According to results of this study, lymph node suppuration was significantly higher in patients who admitted to the hospital more than 14 days after the appearance of symptoms ( $p=0.033$ ). Results of the present study support the importance of making an early diagnosis of tularemia and starting the treatment as early as possible.

In the present study, no statistically significant difference was found between the groups with respect to clinical symptoms and signs namely fever, sore throat, neck swelling, conjunctivitis and rash. However, in patients without symptoms of tonsillopharyngitis at admission, lymph node suppuration was found significantly higher ( $p=0.016$ ). The authors believe that tonsillopharyngitis symptoms may lead to a delay in diagnosis and treatment because they are non-specific. No similar study could be found in the available literature investigating the relationship between clinical symptoms of oropharyngeal tularemia and lymph node suppura-

tion.

Leukocytosis and high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are laboratory abnormalities that can be seen during the course of tularemia. In most studies, ESR and CRP elevations have been reported among tularemia patients.<sup>18,19</sup> Although these inflammatory markers were found higher in patients with lymph node suppuration, the differences were not statistically significant.

This study has some limitations. First, this is a retrospective study with small sample size. Second, there was some missing data for a few patients. Third, the results obtained in this study reflect the status of two cities in Turkey; hence, cannot be generalised to the whole country. Finally, the effect of antibiotics on lymph node suppuration was not evaluated. Thus, more comprehensive studies are needed to demonstrate the relationship between antibiotic initiation time and lymph node suppuration in these cases.

## CONCLUSION

Oropharyngeal tularemia may cause sporadic or epidemic disease in various parts of the world. Antimicrobial initiation time is crucial in oropharyngeal tularemia cases, since lymph nodes may be suppurated in case of more than 14 days' delay in proper treatment. Moreover, absence of tonsillopharyngitis may lead to a delay in the diagnosis of oropharyngeal tularemia. In order to prevent supplicative lymphadenitis, the authors suggest appropriate antimicrobials to be started in oropharyngeal tularemia cases within 14 days after the appearance of symptoms.

### ETHICAL APPROVAL:

This study was approved by the local Ethics Committee of Medical Faculty, Duzce University, Duzce, Turkey (Decision No. 2019/260).

### PATIENTS' CONSENTS:

Informed consents were obtained from all individual participants included in the study.

### CONFLICT OF INTEREST:

The authors declared no conflict of interest.

### AUTHORS' CONTRIBUTION:

NI, HTG: Concept, design, supervision, data collection and processing, interpretation, literature search, writing manuscript, and critical reviews.

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