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Original Article / Çalışma - Araştırma

Clinical and laboratory findings of tularemia: a retrospective analysis

Tularemi hastalığının klinik ve laboratuvar bulguları: Retrospektif bir inceleme

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Objectives: This study aims to define demographic characteristics and clinical and laboratory findings of the patients with tularemia and to assess the treatment outcomes.

Patients and Methods: A total of 58 consecutive patients (26 males, 32 females; mean age 37±22 years; range 6 to 80 years) with tularemia were retrospectively analyzed in this study. Demographic characteristics, laboratory findings, physical examination findings and treatment outcomes were recorded.

Results: Forty patients (86.2%) had glandular tularemia; seven (12.1%) had oropharyngeal tularemia, and one (1.7%) patient had oculoglandular tularemia. The most common symptoms were swollen neck lymph nodes high fever and sore throat. Fifty seven patients (98.2%) had swollen neck lymph nodes; 39 (67.2%) patients had high fever (67.2%) and 36 (62.1%) patients had sore throat. Complete recovery was obtained in 45 patients (77.6%), while 13 (22.4%) were unresponsive to the treatment. The most frequent laboratory findings were high level of C-reactive protein (CRP) and increased erythrocyte sedimentation rate (ESR). Mean leukocyte counts, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea and creatinine levels were within normal range in all patients.

Conclusion: Tularemia should be differentiated from upper respiratory tract infections and cervical lymphadenopathy. The most commonly used hematological and biochemical assays do not provide significant benefits for the diagnosis of tularemia. However, increased level of ESR and CRP at one month may support the diagnosis. Early diagnosis and appropriate treatment may prevent therapeutic failure.

Key Words: Clinical findings; demographic characteristics; laboratory findings; treatment; tularemia.

Amaç: Bu çalışmada tularemia hastalarının demografik özellikleri ve klinik ve laboratuvar bulguları tanımlandı ve tedavi sonuçları değerlendirildi.

Hastalar ve Yöntemler: Çalışmada toplam 58 ardışık tularemi hastası (26 erkek, 32 kadın; ort. yaş 37±22 yıl; dağılım 6-80 yıl) retrospektif olarak incelendi. Demografik özellikler, laboratuvar bulguları, fizik muayene bulguları ve tedavi sonuçları kaydedildi.

Bulgular: Hastaların kırkında (%86.2) glandüler tularemi, yedisinde (%12.1) orofarengeal tularemi, birinde (%1.7) ise okülоglandüler tularemi vardı. En sık görülen semptomlar boyunda lenf düğümü büyümesi, yüksek ateş ve boğaz ağrısı idi. Elli yedi hastada (%98.2) boyunda lenf düğümü büyümesi, 39 hastada (%67.2) yüksek ateş, 36 hastada (%62.1) boğaz ağrısı görüldü. Kırk beş hasta (%77.6) tamamen iyileşirken, 13 hasta (%22.4) tedaviye yanıt vermedi. En sık görülen laboratuvar bulguları, yüksek C-reaktif protein (CRP) düzeyi ve artmış eritrosit sedimentasyon hızı (ESR) idi. Bütün hastalarda ortalama lökosit sayısı, aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), üre ve kreatinin değerleri normal sınırlarda idi.

Sonuç: Tularemi, üst solunum yolu enfeksiyonları ve servikal lenfadenopatiden ayırt edilmelidir. En sık kullanılan hematolojik ve biyokimyasal incelemelerin, tularemi tanısında anlamlı bir katkısı bulunmamaktadır. Bununla birlikte, birinci ayda ESR ve CRP değerlerindeki yükselme tularemi tanısını destekler niteliktedir. Erken tanı ve uygun tedavi ile tedavi başarısızlığı önlenebilir.

Anahtar Sözcükler: Klinik bulgular; demografik özellikler; laboratuvar bulguları; tedavi; tularemi.

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Tularemia is an infectious zoonosis caused by *Francisella tularensis (F. tularensis)* which a gram-negative, aerobic, facultative intracellular bacterium *F. tularensis* has two biotypes: Biovar *F. tularensis* (Jellison type A) originates from rodents and is seen only in North America.[1,2] Type A tularemia may lead to significant complications including rhabdomyolysis, septic shock, pneumonia.[3] *F. tularensis* biovar palaearctica (Jellison type B) is less virulent than *F. tularensis* biovar tularensis (type A) and is commonly seen in European and Asian countries.[4] *F. tularensis* can be transmitted to humans by arthropod vectors (e.g. ticks, mosquitoes, horse, fleas), ingestion of contaminated food or water, and inhalation of aerosolized organisms.[5-7] The course of this disease depends on the *F. tularensis* biovar type, patient's immune status, the route of entry to the body, the extent of systemic involvement and the onset of treatment.[2]

Tularemia is seen in six forms classified according to the route of entry, which are ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, and typhoidal tularemia forms.[8] The aim of this study was to describe some demographic, clinical and laboratory characteristics and to evaluate treatment aspects of disease, in patients with tularemia.

PATIENTS AND METHODS

The Ethical Committee of Erciyes University, Medical Faculty, approved the study.

Patients

The study included 58 consecutive patients (26 males, 32 females; mean age 37±22 years; range 6 to 80 years) with tularemia who were diagnosed and treated at the Department of Otorhinolaryngology of Gaziosmanpaşa University Medical Faculty and Tokat State Hospital between January 2007 - December 2010. Tularemia was suspected in individuals living in the epidemic zone who presented with the findings of fever, pharyngitis or tonsillitis and/or cervical lymphadenopathy and who did not respond to penicillin treatment. Demographic and laboratory data, therapeutic features, the time and pattern of onset of the disease symptoms, physical examination findings and other relevant clinical particulars of the patients with confirmed tularemia diagnosis were collected for all patients according to the study protocol. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total leukocyte and differential blood cell count, levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, polymerase chain reaction (PCR) and serological test for tularemia were recorded in all patients.

Diagnosis of tularemia

Blood specimens were obtained from all patients with suspected tularemia. Patient's diagnoses were confirmed by serology and PCR. The microagglutination method was used for serological diagnosis. Antibody titers of 1:160 and above or positive PCR were accepted to be significant for diagnosis.[9] In our patients, a granulomatous inflammation was observed in the histopathological examination of specimens taken from the cervical lymphadenopathy.

Definition

Improvement was defined as complete regression of patient's symptoms and clinical findings and reduction in lymphadenopathy without suppuration. Therapeutic failure was defined as the persistence or recurrence of symptoms and clinical findings attributable to the disease. Besides, increase in patient's body temperature and increase in parameters associated with the acute phase of the infection such as CRP, increased size in the preexisting lymphadenopathy or occurrence of new lymphadenopathies and drainage of lymphadenopathy following size increase were also defined as treatment failure.

Treatment and follow-up

The patients were hospitalized or were followed up on an outpatient basis until clinical improvement was achieved. Patients were treated with antibiotics. The regimens included the following: oral doxycycline (100 mg every 12 h), intramuscular streptomycin (1 g every 12 h), ciprofloxacin oral (500 mg every 12 h). After the treatment period, patients were recalled for the first control visit two weeks later and then at 4, 8 and 12 weeks. Patients who did not respond to treatment or whose symptoms and physical examination findings did not improve with treatment were followed up more frequently and monitored for up to three months.

Statistical analysis

Categorical variables were presented as count and percentages. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal. Normally distributed variables were presented as mean and

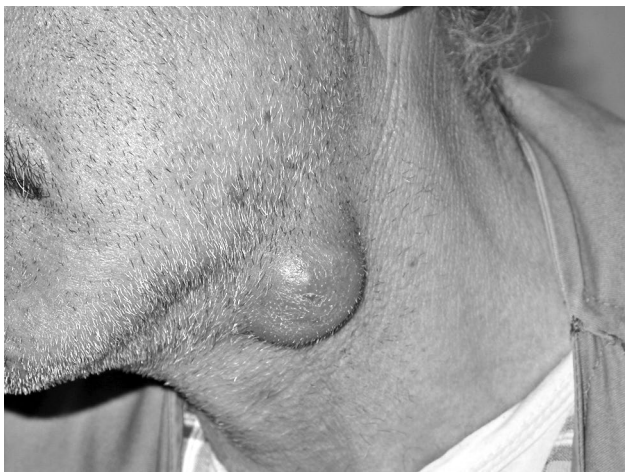

Figure 1. *Glandular tularemia.*

standard deviation (SD). Abnormally distributed variables were expressed as median and interquartile range (Q1-Q3). Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) software 15.0 for Windows was used for all statistical analysis.

RESULTS

Clinical presentations and treatment

Fifty (86.2%) of the patients had glandular tularemia (Figure 1), seven (12.1%) patients had oropharyngeal tularemia (Figure 2) and one (1.7%) patient had oculoglandular tularemia (Table 1). Fifty (86.2%) patients presented to our clinic between January and April and the remaining eight (13.8%) patients presented during other months. The highest number of admissions occurred during February, with 19 (32.8%) of the patients presenting in this month. Thirty-four (59%) patients had a history of previous treatment with the beta-lactam group of antibiotics without benefiting from therapy. The commonest symptoms in our patients were swelling in the neck, fever and sore throat. Fifty-seven (98.2%) patients had swelling in the neck, 39 (67.2%) patients had fever (67.2%) and 36 (62.1%) patients had sore throat. Other symptoms and examination findings of the

Table 1. Clinical forms of 58 patients with tularemia

	n	%
Oropharyngeal	7	12.1
Glandular	50	86.2
Oculoglandular	1	1.7

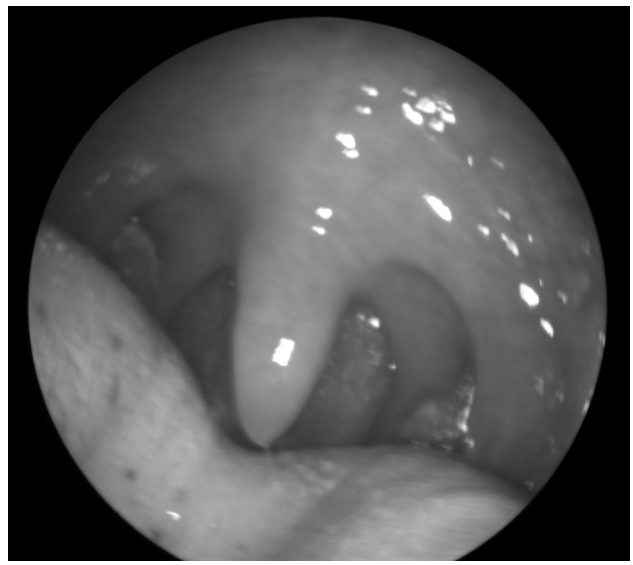

Figure 2. *Oropharyngeal tularemia.*

patients with tularemia are presented in Table 2. Nineteen (32.7%) patients were treated with streptomycin and 38 (65.6%) patients were treated with streptomycin and doxycycline for 14 days. One (1.7 %) patient was treated with ciprofloxacin for 14 days since streptomycin was contraindicated in this patient due to vestibular symptoms. Complete recovery was obtained in 45 (77.6%) patients while therapeutic failure occurred in 13 (22.4%) patients. All patients with therapeutic failure had glandular tularemia and the onset of treatment was late in these patients (12-33 days). Surgical drainage was performed since no reduction in lymphadenopathy could be achieved with medical treatment. All patients recovered completely during the three-month follow-up after surgery.

Laboratory tests

The main biological data are shown in Table 3. The most common laboratory findings were high CRP and ESR levels. Mean leukocyte counts, AST, ALT,

Table 2. Symptoms of patients with tularemia (n=58)

	n	%
Cervical lymphadenopathy	57	98.2
Fever	39	67.2
Sore throat	36	62.1
Weakness	13	22.4
Headache	17	29.3
Weight loss	6	10.4
Ocular burning/itching	1	1.7

Table 3. Laboratory findings of patients with tularemia (n=58)

	Tularemia patients	
	Mean±SD	Range
White blood cell (mm^3)*	8445±2269	
Hemoglobin (g/dL)*	13±1	
Erythrocyte sedimentation rate (mm/h)*	38±21	
C-reactive protein (mg/L)#	11	4-27
Aspartate aminotransferase (U/L)#	19	15-22
Alanine aminotransferase (U/L)#	14	10-22
Creatinine (mg/dL)#	0.8	0.6-1.0

SD: Standard deviation; * Values are presented as mean±SD; # Values are presented as madian (Q1-Q3).

urea and creatinine levels were within normal ranges in all patients.

DISCUSSION

The first case of *F. tularensis* infection was described in 1911 by McCoy.[10] Several studies on tularemia have been performed to date, most of which were epidemic studies. On the other hand, there are a few studies on clinical and laboratory characteristics of tularemia. The present study evaluated some demographic, clinical and laboratory characteristics and treatment outcomes in patients with tularemia.

Several water borne outbreaks of tularemia have been reported in European and Asian countries such as Kosova, Poland, Sweden, Bulgaria, Turkey, Finland, Scandinavia, Russia, Spain and India.[3-6,9,10-18] Most water-borne outbreaks lead to oropharyngeal tularemia.[10] Oropharyngeal tularemia occurs due to drinking contaminated water and eating contaminated meats. While epidemics associated with tick bites generally occur in summer months, epidemics associated with contaminated water are frequently seen in the autumn and winter months.[19] Meriç et al.[20] investigated demographic and clinical characteristics of 58 patients with oropharyngeal tularemia. The authors reported that the disease was most frequent between January and April, peaking during February. They described consumption of natural spring water as a significant risk factor for oropharyngeal tularemia as evident from their logistic regression analysis. Similarly in our study, outbreaks occurred between the months of January and April, and the number of patients peaked in February. The incubation period of the disease is 2 to 6 days (range 1 to 20 days). After this period, several symptoms occur including fever, headache, swelling in the neck, sore throat, chills, malaise, cutaneous lesions, cough, vomiting, abdominal pain.[21,22] The main signs of oropharyngeal tularemia are exudative stomatitis and pharyngitis, with or without tonsillar inflammation and cervical lymphadenitis.[19] The ulceroglandular and glandular tularemia essentially are seen in the head and neck region.[5] In ulceroglandular tularemia, skin lesions and regional lymphadenopathy develop whereas there is only lymphadenopathy in glandular tularemia.[3] Of our patients, 50 (86.2%) had glandular tularemia and seven (12.1%) had oropharyngeal tularemia. Helvacı et al.[4] studied 205 patients with oropharyngeal and glandular tularemia. All cases presented in the autumn or winter. The commonest symptoms were swelling in the neck, fever and sore throat. 164 (80%) patients had cervical lymphadenopathy, 135 (66%) patients had fever and 170 (58.5%) patients had sore throat. The commonest symptoms in our patients were swelling in the neck (98.2%), sore throat (62.1%) and fever (67.2%). Oculoglandular tularemia occurs as a result of eye contact with the finger contaminated with bacteria. Fever, swelling in the eyelid, photophobia, red conjunctiva and increased lacrimation follows. Preauricular lymphadenopathy may also be seen in these patients.[3] One of our patients had oculoglandular tularemia with fever, swelling of the eyelid, red conjunctiva, preauricular (2x1) and cervical (3x3) painful lymphadenopathy. He presented to our clinic on the 14th day and was administered streptomycin 2x1 intramuscular (i.m) for 14 days. His ocular findings improved and preauricular lymphadenopathy was reduced whereas cervical lymphadenopathy did

not change in size and surgical drainage was performed on the 20th day.

There is no specific laboratory finding in tularemia. Normal or high white blood cell count (WBC) can be seen during the course of this disease.[23] Evans et al.[24] studied 88 patients with tularemia and reported mean WBC of 10.400/mm^3 (5.000-22.000/mm^3) in these patients. In their study with 145 patients with oropharyngeal tularemia, Meriç et al.[23] measured mean WBC count as 9.200/mm^3 (5.300-18.000/mm^3) and reported that WBC would not be of significant diagnostic benefit in tularemia. The most extremely used laboratory parameters of systemic inflammatory disease are the ESR and plasma CRP. Erythrocyte sedimentation rate and CRP levels are associated with the severity of the inflammatory process.[25] Syrjälä[26] reported increased levels of both ESR and CRP in tularemia patients. Another study reported increased levels of ESR in all 145 patients with tularemia (mean value 57 mm/h; range 25-110 mm/h) and 79% of the patients had ESR levels >55 mm/h.[25] Evans et al.[24] reported mild increases in hepatic enzymes in tularemia. In our study, WBC count was 8445±2269, ESR levels were 38±21 mm/h and CRP levels were 11 mg/L during the first month. AST, ALT, urea and creatinine levels were within normal ranges in our patients. In light of these findings, we believe that the common hematological and biochemical assays will not provide significant benefits in the diagnosis of tularemia, while increased levels of ESR and CRP in the first month may support the diagnosis.

Streptococcal and staphylococcal tonsillitis, Epstein-Barr virus infection, diphtheria, tuberculosis, pasteurellosis, Lyme disease, fungal infections, toxoplasmosis and malignant diseases should be considered in the differential diagnosis of otolaryngologic tularemia.[27-29] A positive culture result is the gold standard in the diagnosis of tularemia. This method, however, is rarely used in the diagnosis of the disease since laboratories with biosafety level of 2 or 3 are required and the method frequently yields false negative results. Therefore, the microagglutination test is often performed for the diagnosis of tularaemia.[20] As the test result may be negative in the acute phase, serological tests should be done at least 10 days after the onset of illness.[12] Single titers of ≥160 or a fourfold rise in the microagglutination titers of antibody to *F. tularensis* is of diagnostic value for tularemia.[17,22] Antibody titers were >1:160 in our patients with the tube agglutination assay performed on the 15th day. Respiratory specimens, blood, or PCR for exudates or the *F. tularensis* LPS-resistant ELISA may also be used in the diagnosis or tularemia.[17] Histopathologically, tularemia has chronic granulomatous inflammation characteristics. Epithelioid histiocytes, macrophages, lymphocytes and giant cells may be seen in the lesions.[22] In our patients, a granulomatous inflammation was observed in the histopathological examination of specimens taken from the cervical lymphadenopathy. We requested additional assays from some of our patients for differential diagnosis. Results of these assays were negative.

Aminoglycosides, macrolides, and fluoro-quinolones are used in the treatment of tularemia. Streptomycin is the best option in the treatment of tularemia. Medical treatment should continue for 7-14 days.[30,31] Our patients were treated with antibiotics. Nineteen (32.7%) patients were treated with streptomycin and 38 (65.6%) received streptomycin and doxycycline for 14 days. One (1.7%) patient received ciprofloxacin for 14 days since streptomycin was contraindicated in this patient due to vestibular symptoms. In the present outbreak, recovery was achieved in 45 (77.6%) patients. Therapeutic failure was observed in 13 patients, which involved only patients with late treatment onset (after day 12). Recovery occurred following surgical drainage of the lymph nodes in these patients and no patient died.

In conclusion, tularemia should be considered in the differential diagnosis of patients with upper respiratory system infections and cervical lymphadenopathy who live in the epidemic zone and do not respond to penicillin treatment. The common hematological and biochemical assays will not provide significant benefits in the diagnosis of tularemia, while increased levels of ESR and CRP in the first month may support the diagnosis. Serological tests, PCR, ELISA and culture may be used in diagnosis of tularemia. Aminoglycosides, macrolides, and fluorquinolones play an important role in the treatment of tularemia. Streptomycin is the first choice in the treatment of tularemia. Early diagnosis and appropriate treatment may prevent suppuration of the lymph node. Surgical drainage of lymph node abscesses may be considered in

patients with treatment failure, as its benefit has been demonstrated in our study.

Declaration of conflicting interests

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