Original Article

Evaluation of tularemia cases focusing on the oculoglandular form

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Abstract

Introduction: Tularemia is a zoonotic disease caused by *Francisella tularensis*. The oculoglandular form is one of the rarest forms. In this study, evaluated tularemia patients, focusing on the ocular form and the efficacy of early antibiotic therapy.

Methodology: During a tularemia outbreak, the epidemiological and clinical findings, laboratory assays, and drugs used for the treatment of 48 patients were recorded prospectively. The diagnosis of tularemia was confirmed with microagglutination test (MAT) as well as clinical findings.

Results: The mean age of the subject was 48.6 years; 23 (47.9%) of them were female. Thirty-six (81.25%) patients had clinical presentation compatible with oropharyngeal tularemia, seven (14.58%) with oculoglandular tularemia, and two (4.1%) with ulceroglandular tularemia. The most common symptoms were fever (91.6%) and sore throat (81.2%), and the most common findings were lymphadenopathy (91.6%) and tonsillopharyngitis (81.2%). In the oculoglandular form, fever, lymphadenopathy, periorbital edema, conjunctival injection, and chemosis were found. The most distinctive ophthalmic feature was follicular conjunctivitis and conjunctival epithelial defects. Forty-five cases had positive serological results with MAT. All the patients were treated with antibiotics considered effective against *F. tularensis*, and topical antimicrobial treatment was given to the patients with oculoglandular tularemia. Twenty-six (54.16%) patients, who were admitted within three weeks of the onset of symptoms, recovered without sequel.

Conclusions: During tularemia outbreaks, ocular involvement should be considered carefully. The early administration of appropriate treatment will be more effective in resolving the infection and preventing complications. Along with systemic antibiotic therapy, topical treatment will help recovery.

Key words: tularemia; ocular involvement; tularemia outbreak.

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Introduction

Tularemia is a zoonotic disease caused by the Gram-negative bacterium *Francisella tularensis* [1]. Tularemia is distributed worldwide, but it is primarily found throughout the northern hemisphere and most frequently in Scandinavia, North America, Japan, and Russia. However, tularemia has recently been reported from the former Yugoslavia, Spain, Kosovo, Switzerland, and Turkey [1,2,3]. In Turkey, the first outbreak of tularemia occurred in the European part of the country, and the biggest epidemic occured around Bursa in 1988; other cases were reported from the Western Black Sea Region, Ankara, and more recently from Kocaeli, Konya, Sakarya, and central Anatolia [4,5]. The organism is found in a wide range of animal reservoir hosts and can survive for long periods of time in environmental sources such as water and mud. It is transmitted to humans by various modes, including direct handling of infectious carcasses, ingestion of contaminated food or water, arthropod bites, inhalation of infectious dusts or aerosols, or splashing of infected material into the eyes [1,6]. Depending on the route of entry, tularemia occurs in several clinical forms: glandular, ulceroglandular, oculoglandular, oropharyngeal, intestinal, pneumonic and typhoidal [1,7]. Most cases of naturally occurring tularemia are the ulceroglandular form, involving an ulcer at the inoculation site and regional lymphadenopathy. Variations of ulceroglandular disease associated with different inoculation sites include ocular (oculoglandular) and oropharyngeal disease [8]. Whereas ulceroglandular is the most common form of tularemia, the oculoglandular form is one of the rarest ones, comprising only 3%–5% of all cases [9]. Humans may acquire the oculoglandular form of tularemia through direct contact with infected

materials, often via contaminated hands, or contact with contaminated particles. The clinical presentation is a rare medical condition characterized by unilateral painful, purulent, granulomatous conjunctivitis, associated with homolateral cervical and/or pre or retroauricular lymphadenopathy. In this study, we aimed to evaluate the epidemiological and clinical features of tularemia patients, focusing on the ocular form and on the efficacy of early antibiotic therapy during a tularemia outbreak.

Methodology

During an outbreak of tularemia in Bala, a district in the south of Ankara in Turkey, 48 tularemia cases were followed up in the Infectious Diseases and Clinical Microbiology Department of Ankara Numune Training and Research Hospital, between November 2010 and February 2011. The data, including demographics, history of illness, symptoms, clinical findings, laboratory assays, drugs used for the treatment of patients, and therapeutic response, were prospectively recorded on a form. Informed consent was obtained from all study participants.

Case definition

The tularemia cases were diagnosed according to the World Health Organization's (WHO) case definition [10]. Clinically compatible cases with culture positive results for *F. tularensis* or a fourfold or greater increase in the serum antibody titer were considered confirmed;cases with a single elevated serum antibody titer or a clinical sample test positive by DNA detection were considered probable cases.

Clinical diagnosis

Oropharyngeal tularemia was defined as the presence of pharyngitis or tonsillitis and cervical lymphadenopathy in a patient from an endemic region, who had no response to β-lactam antibiotics after at least 10 days of therapy. Patients with enlarged and painful lymph nodes with apparent ulcers were diagnosed as having ulceroglanduler tularemia, and those with conjunctivitis and regional lymphadenopathy were diagnosed as having oculoglandular tularemia.

Diagnostic tests

Diagnosis was confirmed by the presence of at least one of the following test results: a fourfold or greater increase in the titer between two serum samples obtained three weeks apart with one above the 1/160 threshold with a microagglutination test, and/or a positive result in the polymerase chain reaction (PCR) assay.

Serology was performed using a microagglutination test and PCR with aspirated material in Ankara Refik Saydam Hıfzıssıhha National Reference Laboratory.

Treatment and follow-up

All patients received appropriate antibiotics – either aminoglycoside or fluoroquinolone for at least 10 days or doxycycline for at least 15 days [1,10]. The patients with oculoglandular tularemia were also given topical antimicrobial treatment. Therapeutic failure was defined by the presence of one of the following findings: suppuration and draining (spontaneously or by surgical means) of the involved lymph nodes during and after treatment, an increase in the size of the existing lymphadenopathy, or the appearance of a new lymphadenopathy [12]. The treatment was considered successful if the signs and symptoms disappeared and lymphadenopathy resolved without suppuration. A second antibiotic course with a different regime was given in case of therapeutic failure.

The tularemia cases were followed up at three months.

Results

A total of 48 patients were followed up with tularemia. Among them, 10 (20.8%) patients were considered to be confirmed cases, and 38 (79.2%) patients were considered to be probable cases. As the outbreak analysis was not done on site, the index case was not identified among the cases. The mean age of the subjects was 48.6 (range: 20 to 85) years, and 23 (47.9%) of the subjects were female. Thirty-six (81.25%) patients had clinical presentation compatible with oropharyngeal tularemia, seven (14.58%) with oculoglandular tularemia, and two (4.1%) with ulceroglandular tularemia who had vulvar ulcers (Table 1).

Twelve (25%) out of 48 cases were in the same households. Furthermore, a few drank non-chlorinated water from their private wells, but most of them used contaminated water for sanitary procedures (washing hands and face, using in toilets). None of the patients had a previous history of tularemia.

The average time between the onset of the symptoms and diagnosis was 28.3 (range: 3 to 90) days. The most frequent symptoms were fever (91.6%) and sore throat (81.2%).

Table 1. Epidemiological and clinical findings, treatment and prognosis in 48 tularemia patients during the outbreak in Bala, Ankara, between November 2010 and February 2011

Characteristics	**No. (%) of patients**	
Female gender	23 (47.9)	
Mean age (min-max)	48.6 (20-85)	
Mean time of symptoms before admission (min-max)	28.3 (3-90) days	
Symptoms		
Fever	44 (91.6)	
Sore throat	39 (81.25)	
Swelling on the neck	26 (54.1)	
Ocular burning, itching	7 (14.58)	
Signs		
Lymphadenopathy	44 (91.6)	
Cervical	26 (54.1)	
Submandibular	8 (16.6)	
Cervical and submandibular	6 (12.5)	
Submandibular - preauricular	2 (4.1)	
Cervical - submandibular - preauricular	2 (4.1)	
Inguinal	2 (4.1)	
Tonsillopharyngitis	39 (81.2)	
Conjunctivitis	7(14.58)	
Skin eruption	5 (10.41)	
Mucosal lesion in genital region	2 (4.1)	
Treatment		**Duration (days)**
Ciprofloxacin	25 (52.08)	21
Streptomycin	4 (8.33)	14
Doxycycline	5 (10.41)	21- 40
Streptomycin + ciprofloxacin	5(10.41)	10 + 21
Streptomycin + doxycycline	6(12.50)	10 + 21
Streptomycin + doxycycline + ciprofloxacin	3(6.25)	14 + 21 + 21
Outcome		
No complication	26	
Sequel or complication	22	

Table 2. Clinical and laboratory findings and treatment of 7 ocular tularemia patients during the tularemia outbreak in Bala, Ankara, between November 2010 and February 2011

Case	Age and gender	Duration of symptoms (days)	Fever °C	LAP	Ocular findings	MAT		Treatment and duration	
						1st w	3rd w	Systemic	Topical
1	65 F	7	37.8	Preauricular	Episcleritis	(-)	1/320	*Ciprofloxacin 21 days	Ciprofloxacin gout 4x2 7 days
2	34 M	3	38.7	Jugular left 24x11 mm, right 17x7 mm	Periorbital edema, follicular conjunctivitis conjunctival epithelial defects Secretion	(-)	1/20	**Streptomycin 14 days	Ciprofloxacin gout 4x2 7 days
3	49 M	3	39	Submandibular left 28x12 mm right 22x11 mm; preauricular swelling	Periorbital edema, follicular conjunctivitis conjunctival epithelial defects	(-)	1/80	Streptomycin 14 days	Ciprofloxacin gout 4x2 7 days
4	78 M	21	38	Left parotis 10x10 mm	Periorbital edema, hyperemia	1/320		Ciprofloxacin 21 days	Ciprofloxacin gout 4x2 7 days
5	64 F	4	37	Periauricular and retroauricular 20x10 mm	Periorbital edema, conjunctivitis	1/160		Streptomycin 14 days ***Doxycycline 14 days	Tobramycine gout 4x2 + ointment 3x1 7 days
6	60 M	2	39	Left preauricular 20x20 mm; left jugular, submandibular 19x9 mm multiple	Periorbital edema, Ptosis in left eye, chemosis, purulent secretion, conjunctival hyperemia	1/320		Streptomycin 14 days	Tobramycine gout 4x2 + ointment 3x1 7 days
7	41 M	3	36.5	Right parotitis, right submandibular 20x10 mm	Periorbital edema, hyperemia	(-),	1/80	Streptomycin 10 days Doxycycline 10 days	Ciprofloxacin gout 4x2 7 days

*Ciprofloxacin 2x400 mg/day intravenously for 7 days, then 1,000 mg/day orally 14 days; **Streptomycin 2x1g/day intramuscularly for 3 days, followed by 1g/day intramuscularly; ***Doxycycline 200 mg/day orally

Lymphadenopathy (91.6%) and tonsillopharyngitis (81.2%) were the most frequent signs. The findings of patients with tularemia are summarized in Table 1.

Forty-five cases had positive serological results. The microagglutination test was diagnostic of tularemia (titer ≥ 160) in 35 (72.9%) patients from a single serum sample. A fourfold increase in the antibody titer was determined in ten (20.8%) cases, and three cases with ocular tularemia had low titers, between 1/20-1/80. PCR assay from aspiration material was performed in nine patients. In two patients with titers of 1/640 and 1/1280, the PCR assay was positive.

White blood cell counts were within normal ranges in 30 (62.5%) patients; leukocytosis (> 10,000) was found in 21 (43.75%) patients. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were elevated in 44 (87.5%) and 39 (81.25%) patients, respectively. Brucella agglutination tests and anti-Epstein-Barr virus IgM antibody with enzyme immunoassay were found negative.

Before the diagnosis of tularemia, 20 (41.6%) patients were given beta-lactam antibiotics at a secondary hospital or by family practitioners. Twenty-six patients (54.16%) were admitted within three weeks of the onset of symptoms. Ciprofloxacin, streptomycin, and doxycycline alone or in combination were used in treatment. Treatment included ciprofloxacin 2 x 400 mg/day intravenously for 7 days, then 14 days 1,000 mg orally; streptomycin 2 x 1 g/day intramuscularly for 3 days, followed by 1 g/day intramuscularly for 14 days [1]; and doxycycline 200 mg/day orally for 21–40 days. In case of therapeutic failure, a different regimen was given to the patients after the first course of antibiotic therapy (Table 1).

The rate of oculoglandular tularemia was 14.58% in the patients. The most common symptoms were fever, ocular findings, and lymphadenopathy. In patients with ocular findings, routine eye examinations were performed (including visual acuity, biomicroscopy, and fundoscopy) by a specialist of ophthalmotology. Besides the age and gender of patients, the incubation period, ocular findings, localization of lymphadenopathies, microagglutination test titers, drugs used in treatment, and durations are shown in Table 2. Only one patient had tonsillopharyngitis.

Among the laboratory tests, white blood cell counts were normal, and ESR and CRP values were elevated. The ocular symptoms regressed after 7–10 days of therapy. The patients were followed up for three months and fully recovered.

Discussion

Tularemia is an endemic disease in Turkey. Since the first outbreak in 1936 in the Trakya region, many epidemic or sporadic cases have been reported in our country. After a large-scale outbreak with a total of 205 cases of tularemia was observed around Bursa between 1988–2000, an outbreak occurred in Ankara in 2000 [13,14]. In recent years, increases in the number of outbreaks and cases have been observed in various regions of Turkey. According to data from the Ministry of Health, in the first half of 2010, more than 1,000 cases were reported in 32 cities [15]. Most of the outbreaks in Turkey are thought to be due to contaminated water and food [4,5,16,17,18], and the oropharyngeal form is the most common form of tularemia found in Turkey [1,11,19]. In our patients, oropharyngreal tularemia was the most common (81.2%) form, followed by the oculoglandular (14.58%) and ulceroglandular (4.1%) forms. Most of our patients had fever (91.6%) and sore throat (81.2%) at the onset of the disease. Lymphadenopathy was the most common finding (91.6%), followed by tonsillopharyngitis (81.2%) in our cases. The findings of other cases reported from Turkey are similar to those of our study except the rate of tonsillopharyngitis, which was lower than ours. Erythema nodosum and erythema multiforme-like skin eruptions at a rate of 14% and 3%, respectively, have been reported from Turkey [13,20]; in this study, the rate of skin eruptions was 10.41% (Figure 1).

Figure 1. A skin lesion in a patient with tularemia. Informed consent was obtained for publication of this figure.

The present outbreak was considered waterborne because patients were using non-chlorinated natural spring water that is stored in a reservoir in the center of the district. Most of them used non-chlorinated water for sanitary procedures like washing hands and face, using in toilets, and a few of them used it for drinking.

Oculoglandular tularemia, where the conjunctiva is the initial site of infection [1,21], is a rare condition; because of this, the overall index of suspicion is low, so cases often remain unresolved and are underreported.

The rate of oculoglandular tularemia has been reported to be 3%–5% of all diagnosed tularemia cases in several reports [3,9,10,22]. Also in Turkey, epidemically or sporadically, few cases of oculoglandular tularemia have been reported [13,15,16,18,23]. During the last tularemia epidemic, the oculoglandular form was seen with a rate of 14.6% in our patients. This relatively high rate of ocular involvement can be explained with our awareness of the tularemia epidemic. Besides clinical findings, factors including coming from an endemic region and ocular findings such as periorbital edema, conjunctivitis and lymphadenopathies directed us to ocular tularemia. The affected patients were from the district where the outbreak had occurred, and three were from the same household.

The most common transmission route of ocular tularemia was conjunctival inoculation of *F. tularensis* by touching the eye with a contaminated finger or possibly by exposure to blood or body fluid contaminated with infected animal meat, and by contaminated splashes[1,3,10,24,25]. In our patients, the main mode of transmission of *F. tularensis* was thought to be using contaminated natural spring water for washing hands and face. Oculoglandular tularemia is a painful disease with a short incubation period (3–5 days) [26,27]. In our patients, the time of symptoms before admission was 2–7 days except for one patient, for whom was 21 days. The most common symptoms were fever, ocular findings, and lymphadenopathy. The early complaints were photophobia and excessive lacrimation, foreign body sensation, lid edema, and a painful conjunctivitis in five of the patients. Ocular findings were unilateral and included periorbital edema, conjunctival injection and hyperemia, purulent secretion (Figure 2), episcleritis in one patient, and ptosis in another patient. The physical examination by an ophthalmologist showed follicular conjunctivitis accompanied by conjunctival epithelial defects which were the most distinctive ophthalmic features for ocular tularemia (Figure 3). These findings were compatible with the literature [1,9,10,25,28,29]. The lymphadenopathies were tender and were localized especially in preauricular, postauricular, and less frequently in submandibular and jugular regions. Only one patient with ocular involvement had tonsillopharyngitis.

Diagnosis of tularemia requires a high index of suspicion and most often is made on clinical grounds supported by results of microbial cultures and serologic studies [1]. Although the gold standard of diagnosis of tularemia is the isolation of *F. tularensis*, serologic assays such as the microagglutination test or enzyme-linked immunosorbent assay (ELISA) are preferred to cultures for routine diagnosis of endemic

Figure 2. Tularemia infected eye (patient 3) with periorbital edema and secretion. Informed consent was obtained for publication of this figure.

Figure 3. Picture of a tularemia infected eye (patient 3) with follicular conjunctivitis, conjunctival epitelial defects . Informed consent was obtained for publication of this figure.

tularemia [10,11,21,30]. Serology titers of 1/160 or higher within two to three weeks after onset of clinical disease are considered diagnostic of the disease [29]. In this study, the MAT titers of 35 patients varied between 1/160 and 1/2,560 in the first serum samples. A fourfold increase in the antibody titer was determined in the convalescent sera of 10 out of 13 patients with negative serology at the beginning; these patients were accepted as confirmed cases.

The oculoglandular form of tularemia has a short incubation period, and results of serologic tests of acute-phase samples are often negative [26,27]. In four of our patients, the MAT titers of acute phase sera were negative, whereas the other three had titers of 1/160 and 1/320. The duration of symptoms in these four patients was three to seven days, and it was thought that this length of time was not sufficient for a serological response. In the convalescent sera of these four patients, the MAT titers varied between 1/20 and 1/320 in the third week of the disease. It has been reported that antibiotic therapy given in the early phase of the disease can blunt the serologic response, which could mask the convalescent rise in titer needed to confirm the diagnosis [11]. Negative serology, therefore, should not eliminate the diagnosis of tularemia [5,20]. Among the routine laboratory tests, white blood cell counts were normal, and ESR and CRP values were elevated, as has been reported in the literature [1].

It is known that streptomycin, gentamycin, tetracycline, and fluoroquinolone antibiotics are effective, and that early initiation of these agents is important in effective treatment [1,9,31].While streptomycin is the first choice for the treatment of tularemia, fluoroquinolones offer an additional treatment option, especially with the high bioavailability of oral preparations [3,8,26,32,33]. The general recommendations for length of therapy depends on the antibiotics used. Aminoglycosides and ciprofloxacin are thought to have a low incidence of relapse; therefore, a course of 10 days is recommended. For doxycycline and chloramphenicol, a longer course of 14–21 days is indicated [8-11]. In our patients, streptomycin was given for 10–14 days, and ciprofloxacin for 21 days. While 26 of 48 (54%) patients treated with antibiotics active against *F. tularensis* within the first three weeks of their illness fully recovered, therapeutic failure, related to a delay in the initiation of antibiotics, was observed in 22 (45%) of the cases. These results suggest that antimicrobial therapy initiated within 21 days of the onset of symptoms was a statistically significant risk factor for therapeutic failure and prolonged recovery time [11].

Streptomycin was given as an alternative dose regimen to the patients with the oculoglandular form, as recommended by Penn [1]. Ciprofloxacin was preferred for the other two patients – who were older – due to the problems of ototoxicity and nephrotoxicity. In addition, for conjunctivitis, topical antibiotics such as ciprofloxacin and tobramycine ophthalmic drops and tobramycine ointment were used. Ocular symptoms regressed within 7–10 days of therapy. The patients were followed up for three months and fully recovered without complications. In addition to treatment with systemic antibiotics, local therapy with ciprofloxacin and tobramycin eye drops and ointment resulted in rapid recovery and prevented relapse and the complications of oculoglandular tularemia in our study.

Conclusions

As it is possible to overlook the ocular form of tularemia during outbreaks, in cases of nodular conjunctivitis, ocular involvement should be suspected and additional tests should be performed to rule out this form of the disease. The early administration of appropriate treatment will be more effective in resolving the infection and preventing complications. Along with systemic antibiotic therapy, topical eye drops and ointment help recovery.

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