

Case Report / Olgu Sunumu

Oculoglandular and Oropharyngeal Tularemia: A Case Report and Review of the Literature

Okuloglanduler ve Orofarıngeal Tularemi: Olgu Sunumu ve Literatür Derlemesi

Nefise ÖZTOPRAK, Güven ÇELEBİ, Atilla ALPAY,¹ Ayşegül SEREMET KESKİN, Yasemin KOZLUCA¹

*Departments of Infectious Diseases and Clinical Microbiology and ¹Ophthalmology,
Medical Faculty of Zonguldak Karaelmas University, Zonguldak*

Submitted / Başvuru tarihi: 02.08.2008 **Accepted / Kabul tarihi:** 16.09.2008

Tularemia is caused by a small, Gram-negative, pleomorphic coccobacillus, *Francisella tularensis*. Oculoglandular tularemia is a rare clinical form. There are few reports about oculoglandular tularemia, and less than 20 cases with oculoglandular tularemia have been reported in PubMed up to date. We reviewed the literature about oculoglandular tularemia, and reported a 31-year-old woman with oculoglandular and oropharyngeal tularemia. She admitted to our hospital with a three-week history of sudden onset of fever, fatigue, headache, sore throat, swollen left upper lid, injected and erythematous left eye, epiphora, preauricular nontender lump on the left and generalized aches, but there was no history of eye injury. She was living in a village where tularemia is endemic, but no history of encountering with an animal. The clinical diagnosis of oculoglandular and oropharyngeal tularemia was confirmed by microagglutination test and PCR. She was fully improved on the eighth day of the ciprofloxacin treatment. Tularemia should come to mind in patients with fever, severe throat, conjunctivitis and cervical masses especially unresponsive to penicillin or cephalosporine therapy, coming from a tularemia endemic area.

Key words: Tularemia; eye; tonsillopharyngitis; cervical lymphadenopathy; conjunctivitis.

Tularemia hastalığı küçük, Gram-negatif, pleomorfik kokobasil olan *Francisella tularensis* bakterisi ile oluşur. Okuloglanduler tularemi nadir görülen bir formdur. Okuloglanduler tularemi ile ilgili az sayıda yayın vardır, PubMed taramasında günümüze kadar 20'den az yayın bulunmaktadır. Bu yazıda okuloglanduler ve orofarıngeal tularemi tanısı konulan, 31 yaşında bir bayan olgu sunuldu ve okuloglanduler tularemi ile ilgili yayınlar derlendi. Olgu hastanemize üç haftadır devam eden ani başlangıçlı ateş, halsizlik, baş ağrısı, boğaz ağrısı, sol gözde kızarıklık, üst göz kapağında şişlik, göz yaşında artma ve sol preaurikuler bölgede ağrısız şişlik ve genel vücut ağrısı ile başvurdu, göz travması öyküsü yoktu. Tulareminin endemik olduğu bir köyde oturuyordu, hayvan teması öyküsü yoktu. Klinik bulgularla okuloglanduler ve orofarıngeal tularemi tanısı konuldu, tanı mikroagglütinasyon testi ve PCR ile konfirme edildi. Olgu siprofloksasin tedavisinin sekizinci gününde tamamen iyileşti. Tularemi, ateş, boğaz ağrısı, konjunktivit ve servikal kitlesi olan ve özellikle penisilin veya sefalosporin tedavisine yanıt veremeyen ve tulareminin endemik olduğu bölgeden gelen olgularda akla gelmelidir.

Anahtar sözcükler: Tularemi; göz; tonsillofarenjit; servikal lenfadenopati; konjunktivit.

Tularemia, caused by *Francisella tularensis*, is a widely distributed zoonosis in the world.^[1,2] Transmission of *F. tularensis* to humans generally occurs through the bite of a tick or an animal carrying the agent or contact with contaminated

animal products, aerosol droplets, or ingesting contaminated food or water.^[1] It continues to be responsible for significant morbidity and mortality. Patients usually present at least one of six classic types of tularemia: ulceroglandu-

lar, glandular, oculoglandular, oropharyngeal, typhoidal, or pneumonic.^[1] Whereas ulceroglandular is the most common form of tularemia, oculoglandular form is rarely seen in the world. The first case of oculoglandular tularemia, the least common form of tularemia, was reported in 1913 by Vail.^[1,3] Transmission of the bacteria to eye occurs through introduction into the eye by blood or body fluid from an infected tick swimming in water contaminated with infected animal meat or contact with wild rabbits, hunting dogs, and by contaminated splashes.^[3-6] First, eyelids begin to swell, and then preauricular, submaxillar, the anterior cervical lymph nodes and sometimes the axillar nodes or parotid gland become decidedly swollen and tender.^[3] Early complaints may include photophobia and excessive lacrimation, lid edema and a painful conjunctivitis, with injection, chemosis, and small, yellowish conjunctival ulcers or papules in some patients and changes in visual acuity, but visual loss is rare,^[1] Complications are unusual but those most likely to occur are acute glaucoma, corneal edema and corneal ulcer.^[3,7,8] Herein, we described the epidemiological, clinical and diagnostic features about oculoglandular tularemia by one case and review of the literature.

CASE REPORT

A 31-year-old woman was admitted to our hospital with a three-week history of sudden onset of fever, fatigue, headache, sore throat, swollen left upper lid, injected and erythematous left eye, epiphora, preauricular nontender lump on the left and generalized aches, but there was no history of eye injury. However, she already had been treated with penicillin and 2nd generation cephalosporin orally and tobramycin eye drops for 12 days with a diagnosis of upper respiratory tract infection and bacterial conjunctivitis in another hospital, she did not recover. Afterward, she presented to our hospital since her symptoms still persisted and swelling increased despite antibiotic therapy. As additional history, she had optic atrophy in her right eye for 10 years. She was living in a village in Zonguldak where tularemia is endemic.



Fig. 1. Severe conjunctivitis with periorbital redness and edema on the left eye.

Upon further questioning, she reported that one month prior to her first symptoms, she had eaten unwashed chestnuts in a forest site of her village. She drank spring water from the environment. She had no history of encountering with an animal.

On physical examination she was afebrile and there was a severe conjunctivitis with periorbital redness and edema on the left eye (Fig. 1). The conjunctiva was markedly injected and chemotic. Her tonsils were hypertrophic and hyperemic, and there was yellowish white exudate and ulceration on her left tonsil. She had swollen and nontender preauricular lymph node with a size of 4.5x2 cm, hard surfaced and fixed to the underline tissues with no color change. Furthermore, she had tender, soft surfaced and mobile submandibular (2x1 cm) and anterior cervical (1x1 cm) lymphadenopathy (LAP). The remainder of the physical examination was unremarkable. Admission laboratory findings were; white blood cell 7900/mm³ (43% polymorphonuclear leukocytes (PNL), 44% lymphocytes, 8% monocytes), erythrocyte sedimentation rate 75 mm/ hour, C-reactive protein was negative, chest roentgenograms were normal and tuberculin skin test (5TU) was negative. Preauricular LAP was surgically drained, and the drain material revealed 10-15 leukocytes (70% PNL) on every field, no bacteria in the Gram stain. Routine cultures of the lymph node

Table 1. Demographic, epidemiologic and clinical characteristics of the cases with oculoglandular tularemia

Author	Year/ localization	Age/ gender	Incubation period	Epidemiology	Ocular findings	LAP	Diagnosis based on	Treatment (Duration)
Tokgöz ^[21]	1938 Turkey	ND, Male	3 days	Laboratory exposure	Unilateral (ND), follicular conjunctivitis	Submandibular, preauricular	Culture, Agglutination (1/8000)	None
Golem ^[22]	1945 Edirne, Turkey	22, Male	ND	Exposure to contaminated water	Unilateral (right) conjunctivitis, lid edema	Preauricular, submandibular	Agglutination (1/20)	None
Golem ^[22]	1945 Edirne, Turkey	24, Male	ND	Exposure to contaminated water	Unilateral (right) conjunctivitis	Preauricular, submandibular	Agglutination (1/160)	None
Golem ^[22]	1945 Edirne, Turkey	23, Male	10 days	Exposure to contaminated water	Unilateral (right) conjunctivitis	Preauricular, submandibular	Agglutination (1/160)	None
Lindeke ^[6]	1949 Philadelphia, USA	32, Male	ND	Exposure to wild rabbits	Unilateral (right) conjunctivitis, lids edema, small shallow ulcers, yellow nodules on conjunctiva, superficial corneal opacities	Preauricular, submental, submaxillar	Agglutination (1/2560)	Aureomycin (21 days systemic, 15 days local)
Lindsay ^[3]	1951 Edmonton, Canada	40, Male	30 days	Exposure to contaminated sewer water	Unilateral (right) conjunctivitis, purulent discharge, lids edema	Parotid, submaxillar	Agglutination (1/800)	Streptomycin, aureomycin (ND)
Hughes ^[4]	1965 Kentucky, USA	11, Male	4 days	Exposure to dog-tick	Unilateral (left) conjunctivitis, small amount of purulent exudate, swollen lids	Anterior cervical (tender)	Agglutination (1/1280)	Streptomycin (7 days)
Rodney ^[20]	1970 Iowa, USA	30, Male	4 days	Exposure to rabbits (hunting and cleaning)	Unilateral (left) conjunctivitis, small shallow ulcers and yellow conjunctival nodules	Preauricular	Agglutination (1/320)	Streptomycin (10 days)
Bloom ^[13]	1972 Washington, USA	6, Male	60 days	Exposure to wild rabbits	Unilateral (right) conjunctivitis, small grey papule on palpebral conjunctiva	Preauricular, anterior cervical, submandibular, neck, axilla, inguinal	Agglutination (1/320) and fluorescent antibody test	Streptomycin (7 days)
Guerrant ^[5]	1974 Virginia, USA	67, Female	10 days	Exposure to a tick and squirted blood into her eye	Unilateral (left) conjunctivitis, lids edema	Preauricular, anterior cervical	Agglutination (1/160)	Streptomycin (ND)
Chappell ^[12]	1979 Arkansas, USA	57, Male	Several days	Exposure to a tick (no history of ocular contamination)	Unilateral (right) conjunctivitis, nodules on conjunctiva, purulent discharge, punctuate keratitis	Preauricular, submandibular	Agglutination (1/600)	Streptomycin (14 days)
Halperin ^[11]	1985 Minnesota, USA	10, Male	5 days	Minor eye trauma and swimming in contaminated water (with raw sewage and bird carcass)	Unilateral (right) conjunctivitis, shallow conjunctival necrotic ulcer, yellow conjunctival nodules	Preauricular, submandibular	Culture	Gentamicin (10 days)
Parssinen ^[7]	1997 Finland	58, Female	ND	ND	Unilateral (right) glaucoma, edema and redness in the lid, hyperemia in the conjunctiva,	Inguinal	ELISA (Tularemia IgM, IgG and avidity)	Ciprofloxacin (10 days)
Steinemann ^[10]	1999 Arkansas, USA	82, Female	ND	ND	Unilateral (right) conjunctivitis, corneal ulcer, yellow conjunctival nodules	Preauricular	Agglutination (1/320)	Doxycycline + Gentamicin topical (21 days)
Thompson ^[8]	2000 Iowa, USA	18, Male	21 days	Exposure to a wild rabbit	Unilateral (left) conjunctivitis, ptotic, swollen, erythematous upper lid, granulomatous follicles on the conjunctiva	Preauricular, postauricular, submandibular (tender)	Culture	Streptomycin + Nafcillin (10 days)
Peter ^[9]	2001 Gyula, Hungary	17, Female	21 days	ND	Bilateral conjunctivitis, red eye	Submandibular	Agglutination (1/640)	Streptomycin (ND)

ND: Not described in the literature.

material and conjunctival swab were negative for pyogenic bacteria, acid-fast organisms and fungi. Pathologic examination of drain material revealed mixed type of suppurative inflammation.

On the day of admittance, ampicilline-sulbactam (1 g, q6h, iv) and ciprofloxacin (500 mg q 12h po) treatment were started with a prediagnosis of oculoglandular tularemia, oropharyngeal tularemia, and partially treated orbital cellulites. Response to the treatment was good; periorbital edema and hyperemia regressed on the 2nd day, she was fully recovered on the eighth day of the therapy. Tularemia micro-agglutination test (MAT) was reported as 1/320 positive from the

national reference laboratory for tularemia on the 14th day of the treatment; we stopped ampicilline-sulbactam and continued ciprofloxacin treatment for one week more. However, two new lymphadenopathies emerged in left jugulo-digastric region three weeks after the end of the treatment. One of these LAPs was suppurred spontaneously, and the other one was drained surgically. No culture for *F. tularensis* was performed; however, PCR for *F. tularensis* was positive in all drained lymph nodes but negative in the conjunctival swab material. Eight months after the end of the treatment, except three scar lesions on her left neck, she had no symptoms and clinical findings.

DISCUSSION

Oculoglandular form of tularemia has been rarely reported in the world. We searched PubMed Medline to identify the reports on oculoglandular tularemia in English literature using the keywords "oculoglandular and tularemia" and "eye and tularemia" and detected 26 reports, 17 of which we could reach.^[3-19] We reviewed the reports and detected 11 oculoglandular tularemia cases whose information about demographic, epidemiologic and clinical characteristics was reported.^[3-13] Another case report not indexed in PubMed, was also added into the case list.^[20] In addition, a similar search in Turkish literature revealed four more cases with oculoglandular tularemia (Table 1).^[21,22] Among those 16 cases, 11 were male, four were female, and sex was not reported for one case. Oculoglandular tularemia emerged due to tick bites or contact with infected animal in seven cases, contaminated water in five cases, laboratory exposure in one case and unknown origin in three cases. However, the most common transmission route of tularemia was exposure to contaminated animals or ticks in the literature, the main mode of transmission of *F. tularensis* is thought to be drinking uncontrolled spring water in Turkey.^[15,23-28] Leblebicioğlu et al.^[28] found that drinking spring water from the environment and collecting food from the environment were risk factors for tularemia in a case-control study. Similarly, in our case the most probable ways might be drinking contaminated spring water from environment and eating unwashed chestnut or washing her face by contaminated water. Most of the cases had preauricular, submandibular, submaxillar or anterior cervical LAP as our case. Only one case had axillar LAP, two cases had inguinal LAP. Clinical findings of eye involvement of the cases were conjunctivitis, purulent exudates and ptotic, swollen and erythematous upper lid as seen in our patient. One case had bilateral ocular lesions, others were unilateral. The majority of the reviewed cases were diagnosed by tularemia agglutination test and *F. tularensis* was isolated from three cases. We used MAT to confirm clinical diagnosis in our case.

However, including a little number of tularemia species, recent data showed that tularemia species were sensitive to tobramycin in Turkey.^[29] Our patient used tobramycin eye drops with a diagnosis of bacterial conjunctivitis for 12 days at the initial stage of the disease, but local therapy alone with tobramycin eye drops was not effective to resolve the eye infection. The patient recovered from the disease after systemic antibiotics for tularemia were started. We thought that local therapy alone with tobramycin eye drops was not adequate to recover from oculoglandular tularemia because of systemic involvement of the disease. It is known that if effective treatment of tularemia is delayed, unresponsiveness to treatment, suppuration of the lymph node and relapses occur especially in oropharyngeal form.^[23,24] However, ciprofloxacin which is an appropriate antibiotic for tularemia was used in our case, relapses of the disease and suppurations of the lymph nodes occurred because of therapy delay.

In conclusion, oculoglandular and oropharyngeal tularemia are unusual manifestations of an uncommon infection. Oculoglandular tularemia can be distinguished from other causes of ocular infection primarily by history and physical examination, including a careful ophthalmologic examination, but requires a high index of suspicion. Tularemia should be considered in the differential diagnosis of the cases with tonsillopharyngitis, cervical lymphadenitis and granulomatous conjunctivitis; particularly those not responding to penicillin treatment, early treatment with proper antibiotics should be started.

Acknowledges

Thanks to Andreas Voss and his colleagues in Radboud University, Department of Infection Control and Prevention for finding literatures to set up a review about oculoglandular tularemia.

REFERENCES

1. Penn RL. *Francisella tularensis* (Tularemia). In: Mandell GL, Bennet JE, Dolin R, editors. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*. Philadelphia: Elsevier Churchill

- Livingstone; 2005. p. 2674-85.
2. Ellis J, Oyston PC, Green M, Titball RW. Tularemia. *Clin Microbiol Rev* 2002;15:631-46.
 3. Lindsay WR, Scott JW. Oculoglandular tularemia transmitted from contaminated sewer water. *Can J Public Health* 1951;42:146-51.
 4. Hughes WT. Oculoglandular tularemia: transmission from rabbit, through dog and tick to man. *Pediatrics* 1965;36:270-2.
 5. Guerrant RL, Humphries MK Jr, Butler JE, Jackson RS. Tickborne oculoglandular tularemia: case report and review of seasonal and vectorial associations in 106 cases. *Arch Intern Med* 1976;136:811-3.
 6. Lindeke HI, Maiden SD. Oculoglandular tularemia treated with aureomycin. *J Am Med Assoc* 1950;142:99-100.
 7. Pärssinen O, Rummukainen M. Acute glaucoma and acute corneal oedema in association with tularemia. *Acta Ophthalmol Scand* 1997;75:732-4.
 8. Thompson S, Omphroy L, Oetting T. Parinaud's oculoglandular syndrome attributable to an encounter with a wild rabbit. *Am J Ophthalmol* 2001;131:283-4.
 9. Peter R, Banyai T. Erythema nodosum revealing oculoglandular tularemia. *Dermatology* 2001;202:79-80.
 10. Steinemann TL, Sheikholeslami MR, Brown HH, Bradsher RW. Oculoglandular tularemia. *Arch Ophthalmol* 1999;117:132-3.
 11. Halperin SA, Gast T, Ferrieri P. Oculoglandular syndrome caused by *Francisella tularensis*. *Clin Pediatr (Phila)* 1985;24:520-2.
 12. Chappell CW, Brainard J, Shock JP. Oculoglandular tularemia - a case report. *J Ark Med Soc* 1981;78:128-30.
 13. Bloom ME, Shearer WT, Barton LL. Oculoglandular tularemia in an inner city child. *Pediatrics* 1973;51:564-6.
 14. Kantardjiev T, Padeshki P, Ivanov IN. Diagnostic approaches for oculoglandular tularemia: advantages of PCR. *Br J Ophthalmol* 2007;91:1206-8.
 15. Ozdemir D, Sencan I, Annakkaya AN, Karadenizli A, Guclu E, Sert E, et al. Comparison of the 2000 and 2005 outbreaks of tularemia in the Duzce region of Turkey. *Jpn J Infect Dis* 2007;60:51-2.
 16. Centers for Disease Control and Prevention (CDC). Tularemia transmitted by insect bites--Wyoming, 2001-2003. *MMWR Morb Mortal Wkly Rep* 2005;54:170-3.
 17. Christova I, Velinov T, Kantardjiev T, Galev A. Tularaemia outbreak in Bulgaria. *Scand J Infect Dis* 2004;36:785-9.
 18. Rohrbach BW, Westerman E, Istre GR. Epidemiology and clinical characteristics of tularemia in Oklahoma, 1979 to 1985. *South Med J* 1991;84:1091-6.
 19. Syrjälä H, Herva E, Ilonen J, Saukkonen K, Salminen A. A whole-blood lymphocyte stimulation test for the diagnosis of human tularemia. *J Infect Dis* 1984;150:912-5.
 20. Anderson RA. Oculoglandular tularemia: a case report. *J Iowa Med Soc* 1970;60:21-4.
 21. Tokgöz SK, Golem SB. Tülaemide laboratuvar arařtırmaları. *Türk Hıfzısıhha ve Tecrübi Biyoloji Dergisi* 1938;1:137-53.
 22. Golem SB. Lüleburgaz'da yeni bir tulaemi epidemisi. *Türk Hijyen ve Tecrübi Biyoloji Dergisi* 1945;5:27-38.
 23. Celebi G, Baruönü F, Ayođlu F, Cinar F, Karadenizli A, Uđur MB, et al. Tularemia, a reemerging disease in northwest Turkey: epidemiological investigation and evaluation of treatment responses. *Jpn J Infect Dis* 2006;59:229-34.
 24. Helvacı S, Gedikođlu S, Akalin H, Oral HB. Tularemia in Bursa, Turkey: 205 cases in ten years. *Eur J Epidemiol* 2000;16:271-6.
 25. Karadenizli A, Gurcan S, Kolaylı F, Vahaboglu H. Outbreak of tularaemia in Golcuk, Turkey in 2005: report of 5 cases and an overview of the literature from Turkey. *Scand J Infect Dis* 2005;37:712-6.
 26. Gürcan S, Otkun MT, Otkun M, Arikan OK, Ozer B. An outbreak of tularemia in Western Black Sea region of Turkey. *Yonsei Med J* 2004;45:17-22.
 27. Sahin M, Atabay HI, Bicakci Z, Unver A, Otlı S. Outbreaks of tularemia in Turkey. *Kobe J Med Sci* 2007;53:37-42.
 28. Leblebicioglu H, Esen S, Turan D, Tanyeri Y, Karadenizli A, Ziyagil F, et al. Outbreak of tularemia: a case-control study and environmental investigation in Turkey. *Int J Infect Dis* 2008;12:265-9.
 29. Gurcan S, Karabay O, Karadenizli A, Karagol C, Kantardjiev T, Ivanov IN. Characteristics of the Turkish isolates of *Francisella tularensis*. *Jpn J Infect Dis* 2008;61:223-5.