Francisella tularensis Infection Causing Parinaud Oculoglandular Syndrome

ABCEF 1
Kinga Ilona Nagy
BD 1
Erzsébet Pribelszki
BD 2
Ágnes Sira
BC 3
Borbála Fullajtár
BD 1
Tamás Rácz
ACDEF 1
Tamás Major

Corresponding Author: Tamás Major, e-mail: major.tamas@mfkh.hu
Financial support: None declared
Conflict of interest: None declared

Patient: Male, 66-year-old
Final Diagnosis: Oculoglandular tularemia
Symptoms: Fever • unilateral conjunctivitis • ipsilateral preauricular lymphadenopathy
Clinical Procedure: Surgery • empiric antibiotic treatment
Specialty: Infectious Diseases • Otolaryngology

Objective: Rare disease
Background: Parinaud oculoglandular syndrome is a unilateral granulomatous palpebral conjunctivitis associated with preauricular, submandibular, and cervical lymphadenopathies. Several infectious diseases can cause Parinaud oculoglandular syndrome, usually with a conjunctival entry. The most common underlying pathology is cat scratch disease, followed by the oculoglandular form of tularemia. Diagnosis is usually a serious challenge as these infections are themselves rare. On the other hand, Parinaud oculoglandular syndrome may be a rare manifestation of more common disorders (eg, tuberculosis, syphilis, mumps, herpes simplex and Epstein-Barr virus, adenovirus, Rickettsia, Sporothrix, Chlamydia infections).

Case Report: We present the case of a 66-year-old man with granulomatous conjunctivitis and ipsilateral preauricular, submandibular, and upper cervical lymphadenopathies following a superficial corneal injury. Although the systematic amoxicillin/clavulanic acid and metronidazole antibiotic therapy started immediately at admission, the suppuration of the lymph nodes required surgical drainage. Based on his anamnesis (sheep breeding; a twig scratching his eye 2 days before the initial attendance) and symptoms, a zoonosis, namely the oculoglandular form of tularemia, was suspected, empiric ciprofloxacin therapy was administered, and the patient recovered without sequelae. The Francisella tularensis infection was eventually confirmed by microagglutination serologic assay.

Conclusions: If Parinaud oculoglandular syndrome is diagnosed and cat scratch fever as the most common etiology is not likely, other zoonoses, especially the oculoglandular form of tularemia, should be suspected. Serology is the most common laboratory method of diagnosing tularemia. Empiric fluoroquinolone (ciprofloxacin) or aminoglycoside (gentamicin or streptomycin) antibiotic therapy should be started immediately at the slightest suspicion of oculoglandular tularemia.

Keywords: Francisella tularensis • Lymphadenopathy • Conjunctivitis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/943915

Publisher’s note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.
Introduction

Parinaud ocularglandular syndrome (POGS) is a unilateral granulomatous palpebral conjunctivitis associated with preauricular, submandibular, and occasionally cervical lymphadenopathies. POGS must be distinguished from Parinaud syndrome, the multicausal triad of impaired upward gaze, convergence retraction nystagmus, and pupillary hyporeflexia [1]. Both syndromes were first reported by Henri Parinaud, a French ophthalmologist (3 cases of POGS in 1889) [2]. Several infectious diseases can cause POGS, usually with a conjunctival entry. The characteristic painful or tender lymphadenopathy initially appears in the primary regional lymph node regions of the eyelids. The most common background pathology is cat scratch disease (CSD) caused by Bartonella henselae. The annual incidence of CSD is 2.4-2.7 per 100,000 persons, and POGS occurs in approximately 4.3% of CSD cases [2,3]. The second most common etiology of POGS is the ocularglandular form of tularemia, a further zoonotic bacterial disease [2]. In a review of PubMed and Google Scholar articles by Dixon et al, 39 POGS cases were identified between 1976 and 2020, including 12 cases of CSD and 10 cases of ocularglandular tularemia (OGT) [2]. Diagnosis is usually a serious challenge, as CSD and tularemia are themselves rare diseases, and POGS can be a rare manifestation of more common disorders (e.g., tuberculosis, syphilis, mumps, herpes simplex and Epstein-Barr virus, adenovirus, Rickettsia, Sporothrix, and Chlamydia infections). Accordingly, the diagnostic strategy of POGS starts with the assessment of CSD (feline exposure, B. henselae cultures from conjunctival swabs, serology) [3].

POGS may be significantly underdiagnosed as rare infectious diseases are often missed, particularly in areas assumed to have a low incidence of the given disease [4]. Patients with POGS may recover spontaneously or as a result of symptomatic or empiric antibiotic therapy. On the other hand, these infections can result in serious ophthalmologic and general complications, especially in immunosuppressed patients [5].

In this report we describe a case that clearly demonstrates the difficulties in the multidisciplinary diagnosis of the very rare POGS, the identification of the etiology based on detailed case history and serology, and the immediate effectivity of adequate empiric therapy.

Case Report

A 66-year-old man who was a non-smoker and non-drinker without known co-existing diseases presented at the Emergency Department of our institution with a 2-day history of right ocular redness and purulent discharge, tender right preauricular and cervical lymph nodes, and fever. Two days before the onset of his symptoms, a twig scratched his right eye. Ophthalmologic examination revealed swollen and erythematous right upper and lower eyelids, conjunctival injection, chemosis, corneal erosion, and preserved eye movements. A conjunctival culture was taken, showing the growth of Streptococcus agalactiae 3 days later, sensitive to the later empiric antibiotic therapy. Painful 2-3 cm lymph nodes were palpable in the ipsilateral preauricular, submandibular, and upper cervical regions, without any further abnormalities at ear-nose-throat (ENT) examination. Computed tomography (CT) of the head and neck demonstrated several spherical-shaped lymph nodes with a 5 cm maximum diameter in the right preauricular and cervical IB, II, and III regions, with contrast-enhancing margins, without suppuration. Paranasal sinuses and orbits were intact on CT. Abdominal sonogram and frontal chest radiograms were both normal. White blood cell (WBC) count was 12.8 G/l (normal range: 4-10), C-reactive protein (CRP) was 106.9 mg/l (normal: <10). The patient refused urgent admission. Oral amoxicillin/clavulanic acid therapy (2×1 g) was initiated.

On day 4 after symptom onset, the former right ophthalmologic status (Figure 1) was completed with a granulomatous tissue shining partially up the right cornea. This was removed and sent to histopathology, showing nonspecific conjunctivitis. Levofloxacin and dexamethasone eye drops were started. Due to the poor general condition, fever, and persisting cervical lymphadenopathy (Figure 2), the patient was hospitalized at the ENT Department and empiric combined intravenous amoxicillin/clavulanic acid (3×1.2 g) and metronidazole (2×500 mg) antibiotic therapy was given.

On day 7 after onset, inflammatory parameters showed a mild regression (WBC 9.82 G/l, CRP 77.5 mg/l), but his poor general condition and conjunctival and cervical status did not improve. A repeated cervical CT on day 9 (Figure 3) demonstrated serial central suppuration of the lymph nodes the same sizes and location as at the first examination. At this point, POGS was suspected. The patient did not have contact with cats, but the corneal injury from a twig scratch and his occupation (sheep breeding) raised the possibility of another zoonosis — the ocularglandular form of tularemia. A blood sample was taken for Francisella tularensis and Toxoplasma gondii serologies. The antibiotic therapy was immediately switched to ciprofloxacin (2×400 mg iv). The patient underwent the surgical exploration and drainage of right neck lymph node regions II-III-IB-IA and sampling for histopathology and cultures. The patient’s general condition gradually improved and his inflammatory parameters (WBC, CRP) were normalized by day 14. He was discharged on day 16 with the recommendation of oral ciprofloxacin therapy (2×500 mg) for an additional week.

Culture from the suppurative lymph nodes was negative and the pathological examination revealed necrotizing granulomatous...
inflammation with multinucleated giant cells. Ziehl-Neelsen staining did not show microorganisms in the specimen. Serology demonstrated past toxoplasma infection, while the F. tularen-sis microagglutination assay (day 33) was diagnostic of tularemia in a titer of 1: 160.

Three months after his discharge the patient is asymptomatic.

Discussion

Although the co-existence of the unilateral granulomatous palpebral conjunctivitis associated with preauricular and cervical lymphadenopathies was obvious at the first attendance of our patient, their resistance for the empiric local and systemic antibiotic therapies called our attention to POGS. CSD was
excluded solely by the lack of feline exposure, and B. henselae serology and cultures were not performed. Although in the review of Dixon et al cat/kitten contact was noted in 11 out of 12 B. henselae-induced POGS cases [2], the lack of feline exposure does not exclude CSD, as in a minority of cases B. henselae is transmitted from cats to humans by arthropod vectors (tick and fleas) [6]. This is a limitation of our case report. The role of conjunctival S. agalactiae infection in the etiology of POGS is equivocal, as this microorganism was sensitive to the ineffective empiric antibiotic therapy. Instead of CSD, a further zoonosis, the oculoglandular form of tularemia was suspected, based on the patient’s occupational anamnesis and/or the possible etiologic role of the branchlet slamming into his eye 2 days prior to the first attendance, which corresponds with the short incubation time of tularemia. Initially, the high efficacy of ciprofloxacin, and eventually, the F. tularensis microagglutination assay confirmed the diagnosis of OGT.

Tularemia is a rare and potentially severe zoonosis caused by F. tularensis, an aerobic intracellular Gram-negative coccobacillus. In Europe, all cases reported to date were caused by F. tularensis var. holarctica (type B) [4]. Due to its extreme virulence, F. tularensis is classified as a category A biowarfare agent by the Centers for Disease Control and Prevention (CDC) in the United States [7]. F. tularensis is extremely resistant to environmental stress, surviving for long periods at low temperatures in water, soil, and animal carcasses. F. tularensis is transmitted from animals to humans by direct contact (eg, animal carcasses) or indirectly by arthropod vectors (Ixodes and Dermacentor tick and mosquito species), ingestion of water or food contaminated with infectious carcasses, or inhalation of infectious dusts and aerosols [8]. An abundance of wild (eg, Lagomorpha, Rodentia, fox species, wild boar, raccoon dog) and occasionally domestic mammals can be reservoirs. Tularemia can appear as sporadic cases or outbreaks [8-10]. It is a reportable disease in the European Union (EU) [4]. According to the Annual Epidemiological Report for 2019 of the European Centre for Disease Control and Prevention (ECDC), 415-1463 confirmed cases per year were reported from 2015 to 2019, resulting in a mean annual incidence of 0.3/100 000 persons [11]. Tularemia shows a seasonal pattern, with most cases occurring from July to November. In Hungary, 11-35 cases were reported annually in the above period (incidence of 0.2-0.4/100 000, corresponding to the mean EU average). The EU male-to-female ratio in 2019 was 1.5: 1. Notification rates increased with age, peaking at 45-64 years [11].

Clinical manifestations depend on the infection route, strain virulence, infective dose, and host immunity. Following an incubation period of 3-5 days, the disease manifests with acute flu-like symptoms (fever, chills, fatigue, myalgia, and headaches) [9]. In the ocular-glandular form, the route of transmission is highly variable (eg, directly by hands contaminated at flaying of infected animals, indirectly by periorcular arthropod bites, or swimming or bath in contaminated water) [12-14]. Lakos et al report an OGT acquired after crushing a tick removed from a dog [15]. In our case the twig scratching the patient’s right eye could have contributed to inoculation of the infectious agent. In our patient, possible routes of transmission include the twig being contaminated with infected water, aerosol transmission, and direct contact with sheep. In the literature, only 1 case of ulceroglandular tularemia is described with a proven transmission route via shearing sheep [16].

The most common method of OGT diagnosis is microagglutination serologic assay. Titors of ≥1: 160 within 2-3 weeks after the onset of symptoms or a 4-fold increase in microagglutination test titers over a 2-week interval (between acute and convalescent sera) are considered diagnostic of tularemia [12]. Specific antibodies become detectable between 10-14 days following the onset of disease [17,18]. In addition, adequate antibiotic therapy given in the early phase of the disease can blunt the serologic response, resulting in a false-negative test result [8]. According to a recent review article, serology was the most frequently applied diagnostic test of OGT [13]. As an alternative or a supplement to serology, polymerase chain reaction (PCR) specific to the 16S rRNA or the tul4 and fopA bacterial genes is suggested. The advantages of PCR are its applicability in a wide range of samples (conjunctival swabs, fine-needle aspiration biopsy specimens, and fresh-frozen or formalin-fixed and paraffin-embedded tissues), and its sensitivity and specificity, enabling the early confirmation of OGT [17]. Detection of F. tularensis antigens from swabs, lymph node aspirates, or tissue biopsies is feasible by direct immunofluorescence assay [10,19] and allows for independent titration of IgM and IgG immunoglobulin classes but relies on subjective fluorescence reading only [20].

Histopathological examination by itself is not specific for OGT, but it may be helpful in differential diagnosis (eg, tuberculosis, cat scratch disease, Rosai-Dorfman disease) [21]. Conventional aerobic cultures from conjunctival swabs are not routinely recommended in the diagnosis of OGT because of the low isolation rate (5%) [12]. F. tularensis, although extremely resistant to environmental stress, is very fastidious if cultured, needing special growth conditions (cysteine-enriched media and long culture time) [5]. In addition, because it is highly contagious, its culture is a potential hazard to laboratory personnel, necessitating Biosafety Level 2 precautions [13].

Based on the case definitions of the World Health Organization (WHO) guidelines of tularemia, our patient was considered as “presumptive” for tularemia (suggestive clinical symptoms and a single positive serum) [22]. According to the tularemia (Francisella tularensis) 2017 case definition by the CDC, our patient was a “supportive” case [23]. The “confirmed” (WHO)
or “confirmatory” (CDC) case definition would have required the isolation of *F. tularensis* in clinical specimens or the 4-fold or greater change in serum antibody titer to *F. tularensis* antigen between acute and convalescent sera [22,23].

The first-line treatment of tularemia is streptomycin or gentamicin, especially in generalized cases, while in milder cases quinolones and doxycycline may be the best choices [24]. In North America, where type A causes severe disease, streptomycin is preferred, while in Europe, where exclusively type B disease has been detected so far, most authors recommend ciprofloxacin either in intravenous (2×400 mg) or oral (2×500 mg) routes of administration [13,19]. The duration of ciprofloxacin therapy depends on symptoms, but a minimum of 10-14 days is suggested [8]. To prevent possible complications, adequate antibiotic therapy should be started immediately at the slightest suspicion of tularemia [15]. Beta-lactams are not indicated, although several authors mention their empiric administration between the onset of the disease and the suspicion of tularemia [8,12-15,25].

The suppuration of cervical lymph nodes is a local complication of OGT [12,13]. Surgery (drainage or resection of the affected lymph nodes) is indicated when there is no response to a second course of antibiotics and when suppuration of lymph nodes or invasion of the neighboring tissue is observed [19]. In our case, lymph node suppuration detected by the repeated neck CT accounted for surgery. The involvement of lymph nodes regions other than the preauricular and submandibular ones is unusual in OGT and might suggest the combined ocularoglandular and oropharyngeal forms of tularemia, although the pharynx was not affected in our patient. Ophthalmological complications of OGT are dacryocystitis, uveitis, optic neuritis, and loss of vision [12,13]. In generalized OGT, cutaneous changes (e.g., maculopapular or vesiculopapular eruptions, erythema nodosum), osteomyelitis, pneumonia, and meningitis may occur [12,25].

In tularemia the average time between the onset of symptoms and diagnosis is 28-30 days [8,9]. In a recent review analyzing 19 OGT cases, this interval was 41 days [13]. In our case, the times from disease onset to OGT suspicion and serological diagnosis were 9 and 33 days, respectively.

Based on the incidence of tularemia in Europe (0.3/100 000), the frequency of OGT among tularemia cases (5%), and the population of Hungary (9.6 million in 2023), 1 or 2 OGT cases per year are expected in our country.

**Conclusions**

POGS should be suspected if unilateral granulomatous palpebral conjunctivitis and ipsilateral preauricular and submandibular lymphadenopathies are observed. If cat scratch fever as the most common etiology is not likely based on the case history, serology, and cultures, other zoonoses, especially the ocularoglandular form of tularemia, should be suspected. Tularemia diagnosis is based on serology in most cases. To fulfil confirmed diagnosis of OGT, the verification of a 4-fold or greater change in antibody titer to *F. tularensis* antigen between acute and convalescent sera or the isolation of *F. tularensis* are needed. Empiric fluoroquinolone (ciprofloxacin) or aminoglycoside (gentamicin or streptomycin) antibiotic therapy should be started immediately at the slightest suspicion of OGT.

**Declaration of Figures’ Authenticity**

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

**References:**

13. Copur B, Surme S. Water-borne ocularoglandular tularemia: Two complicated cases and a review of the literature. Travel Med Infect Dis. 2023;51:102489