The Journal of Laryngology & Otology (2009), ***123***, *1252–1257*.

doi:10.1017/S0022215109004757

Clinical Record

Tularaemia of middle ear with suppurative lymphadenopathy and retropharyngeal abscess

R Gürkov, U Kisser, W Splettstösser*, M Hogardt†, E Krause

Abstract

Objective: We report an extremely rare case of otitis media due to *Francisella tularensis*, complicated by multiple suppurative cervical lesions and a lasting conductive hearing loss.

Case report: A young woman presented with otitis media, several neck swellings and a retropharyngeal swelling. Polymerase chain reaction testing of aspirated fluid and serology confirmed the diagnosis of tularaemia. Specific antibiotic therapy initiated six weeks after the onset of initial symptoms did not resolve the disease, and open surgical drainage was necessary.

Conclusions: Otitis media unresponsive to conventional therapy and accompanied by unusually pronounced lymphadenopathy should prompt the clinician to consider tularaemia as a differential diagnosis, in order to initiate timely, specific therapy.

Key words: Francisella Tularensis; Otitis Media; Lymphadenitis; Otolaryngology

Introduction

Tularaemia is a rare zoonosis caused by the Gram-negative coccobacillus *Francisella tularensis*. Human disease is primarily associated with two subspecies: *F tularensis tularensis* (type A), which is highly virulent and found only in North America; and the less virulent *F tularensis holarctica* (type B), which is thought to be endemic throughout the northern hemisphere.[1,2] In Germany, there are an average of three new cases of tularaemia per year.[3] Depending on the route of infection, different forms of tularaemia can be distinguished. After animal bites (from rodents or cats) or transmission by ticks or mosquitoes, the ulceroglandular form occurs, involving skin lesions, fever and lymphadenopathy.[4] Glandular tularaemia is characterised by lymphadenopathy without an identifiable skin lesion. Airborne infection can cause pneumonic tularaemia,[5] while inoculation of the conjunctiva leads to the oculoglandular form.[6] Oropharyngeal tularaemia only accounts for 1–4 per cent of all cases and can be acquired by exposure to contaminated water or consumption of poorly cooked meat (e.g. hares and rabbits).[7] Typical manifestations include painful pharyngitis, fever and cervical lymphadenopathy. Acute otitis media is an extremely rare presentation of this disease. To the best of our knowledge, only a single case of tularaemia in the middle ear has been reported to date.[7]

Here, we describe the case of a 27-year-old woman who presented with acute otitis media and prolonged suppurative cervical lymphadenopathy due to infection with *F tularensis holarctica*.

Materials and methods

Pus and aspirate taken from several suppurative lesions were cultured on cysteine heart agar, according to standard protocols for this fastidious pathogen.[8] Specimens from assumed sterile sites were additionally incubated in a blood culture system (Bactec BD, Heidelberg, Germany) for 21 days. Deoxyribonucleic acid (DNA) was extracted from aspirate using the DNeasy blood and tissue kit (Qiagen, Hilden, Germany). Polymerase chain reaction amplification and product detection were performed in a LightCycler instrument (Roche, Mannheim, Germany). For 16S rDNA polymerase chain reaction amplification, the oligonucleotide primers fD1 (5′ AGAGTTTGATCCTGGCTCAG 3′; where A = adenine, G = guanine, T = thymine and C = cytosine) and 800R (5′ GAGTACCAGGGTATCTAATCC 3′) were used, which target a region of the 16S ribosomal ribonucleic acid gene of eubacteria. In order to identify the resulting 800 bp amplicon, the product was purified and subjected to automated sequencing using primer 800R (Agowa GmbH, Berlin, Germany). The nucleotide sequence of the amplicon was matched to existing GenBank sequences by nucleotide–nucleotide Basic Local Alignment Search Tool analysis, which allowed identification of francisella species specific DNA up to species level. Real-time polymerase chain reaction protocols targeting the *16S rRNA* gene and *fopA* gene were performed as recently described.[8,9] Conventional polymerase chain reaction protocols[10,11] were used to confirm the presence of the holarctica subspecies. Serum samples from the patient were examined by enzyme-linked immunosorbent assay and immunoblot, as recently described.[12]

Case report

A 27-year-old, previously healthy woman was admitted to the ENT clinic at the Munich university hospital

From the Department of Otorhinolaryngology Head and Neck Surgery and the †Max von Pettenkofer Institute for Hygiene and Medical Microbiology, University of Munich, and the *Institute of Microbiology, Federal Armed Forces Medical Academy Munich, Germany.
Accepted for publication: 10 November 2008. First published online 2 March 2009.

complaining of a feeling of pressure in the left ear, with accompanying hearing loss and periauricular swellings.

On physical examination, tender, fluctuating masses in the left preauricular and laterocervical regions were found (Figure 1), along with a fluid accumulation, possibly suppurative, behind the tympanic membrane. Oral examination revealed a bulging, retropharyngeal mass behind the right posterior palatine arc (Figure 2).

Audiometric tests showed a conductive hearing loss of 15–30 dB (Figure 3). Tympanometry revealed reduced compliance of the sound conduction apparatus (Figure 4). Laboratory tests revealed a white blood cell count of 9.2×10^9/l and a C-reactive protein (CRP) concentration of 36 mg/l (reference range: <5 mg/l). Ultrasound examination of the neck revealed a phlegmoneous inflammation of the soft tissue around the left sternocleidomastoid muscle. Tuberculosis screening was negative.

Thirty-five days prior to presentation, the patient had begun to have symptoms of a sore throat (which had lasted three days, days zero to three), ear pain (which lasted four weeks, days zero to 28) and a feeling of pressure in the ear. One week after onset of symptoms, fever occurred (days seven to 14), and another week later (day 14) laterocervical and periauricular swellings developed which were only mildly painful.

Before the patient had been referred to our hospital, her local ENT specialist had performed computed tomography and magnetic resonance imaging (MRI) scans. These scans had revealed multiple suppurative lesions, including mastoiditis, a preauricular and an infra-auricular abscess, phlegmoneous inflammation of the laterocervical soft tissue (all on the left side), and a retropharyngeal abscess on the right side (Figures 5 and 6).

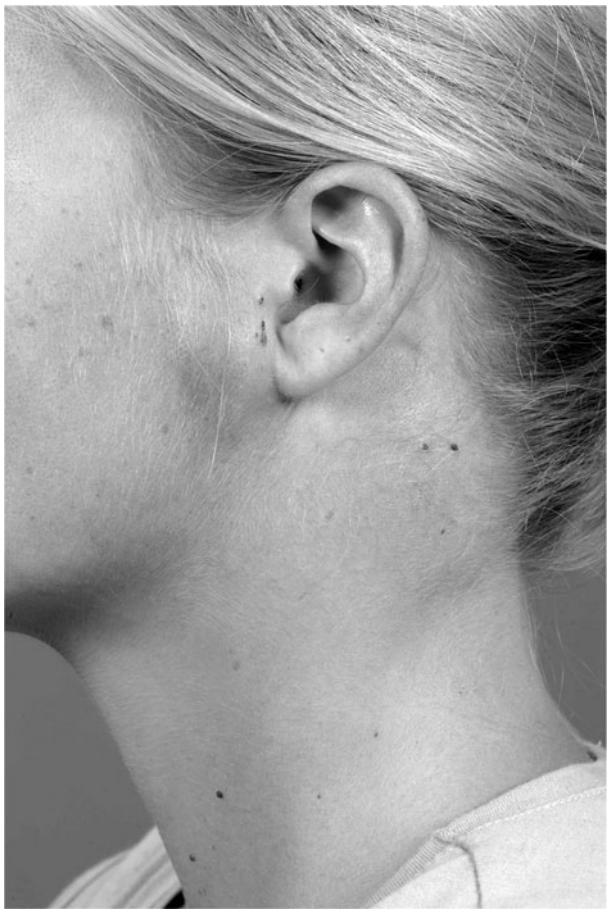

FIG. 1

Preauricular and laterocervical swellings found on initial presentation.

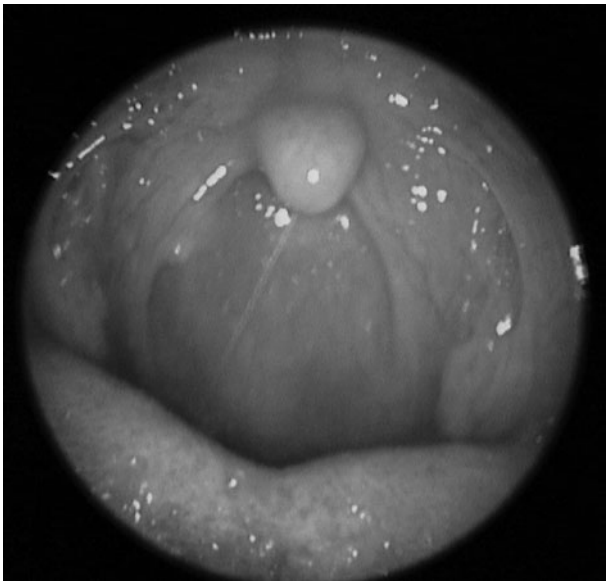

FIG. 2

Oral endoscopic view of right retropharyngeal abscess. Note the bulging of the right posterior pharyngeal wall, displacing the right posterior palatine arc craniolaterally.

The patient had been commenced on oral amoxicillin (days seven to 16) and oral cefuroxim (days 17 to 34). On day 25, the patient had noticed multiple, tender, bruise-like, erythematous eruptions on her left shin, probably representing erythema nodosum, which lasted for 10 days.

In our hospital, the patient received intravenous ceftriaxone (days 35 to 44) as empirical therapy. As there was no regression in the lymphadenopathy, as evidenced by repeated ultrasound examination, the enlarged cervical lymph nodes were aspirated on day 41 and the aspirates sent for microbiological analysis. Since conventional microbiological cultures were negative, the aspirate specimens were subjected to eubacterial polymerase chain reaction analysis, which yielded a positive result. By using 16S DNA sequencing, the polymerase chain reaction amplicon was identified up to genus level as francisella species specific DNA. For definitive species identification, the DNA extract and aspirate were subjected to real-time polymerase chain reaction, resulting in the diagnosis of *Francisella tularensis* subspecies *holarctica*.

Serological detection of high immunoglobulin (Ig) M and IgG titres against *F tularensis* Lipopolysaccharide (1:12 800 and 1:6400, respectively) confirmed a diagnosis of acute tularaemia in our patient. Therefore, the patient was commenced on intravenous ciprofloxacin combined with oral doxycycline (days 44 to 50), followed by oral ciprofloxacin (days 51 to 69). Repeated punctures of the suppurative cervical lymph nodes were performed. On day 45, the CRP level was 8 mg/l.

Despite intensive anti-bacterial therapy and repeated needle aspiration of the suppurative lesions, no clear improvement was seen on repeated MRI scans, ultrasound examinations, audiometric tests and tympanometry. On the contrary, the laterocervical cellulitis evolved into an abscess (Figure 7). Consequently, intravenous gentamicin therapy was commenced (days 55 to 69). Even with such therapy, the patient's symptoms were not relieved to a satisfactory degree. Thus, definitive, open surgical drainage of all the suppurative lymph nodes was undertaken, followed

https://doi.org/10.1017/S0022215109004757 Published online by Cambridge University Press

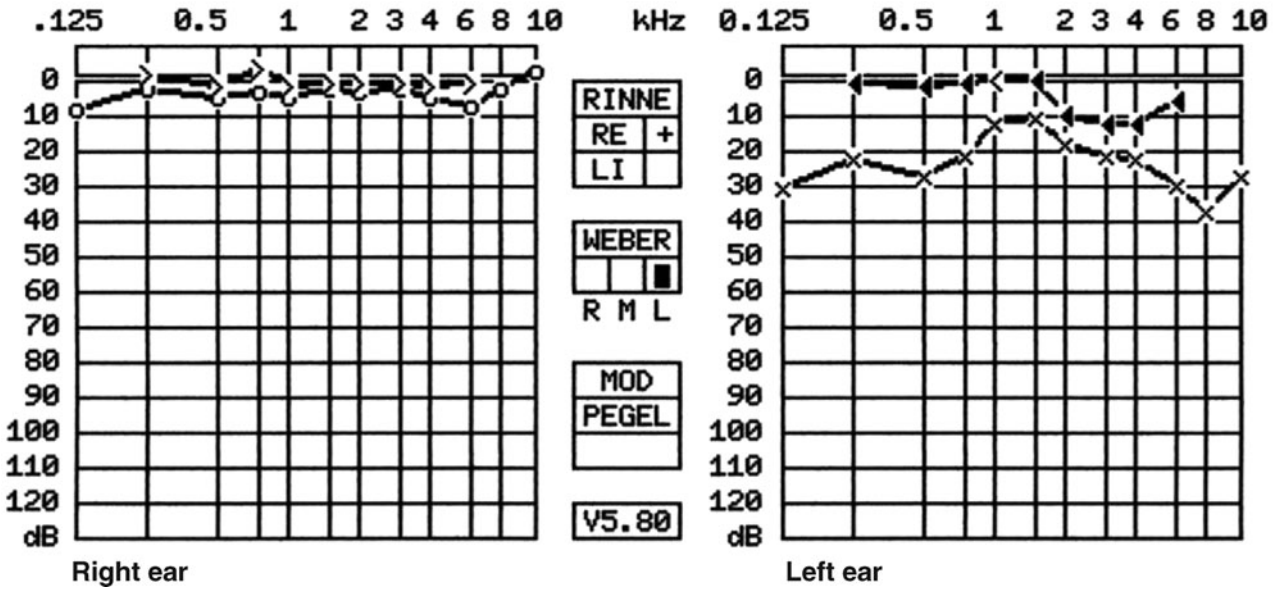

FIG. 3
Pure tone audiogram showing conductive hearing loss of the left ear.

by daily irrigation. Paracentesis was conducted in order to relieve the feeling of pressure in the middle ear, revealing no significant fluid collection in the tympanic cavity.

On day 69, the patient was discharged with a CRP level of 3 mg/l (reference range: <5 mg/l).

Over the following six months, the patient was seen several times for follow up. Repeated audiometry revealed a persistent, mild, conductive hearing loss of about 15 dB, corresponding to an unchanged, mild, subjective auditory impairment, although otomicroscopy showed no pathological findings. At the time of writing, the patient did not wish to undergo further tympanoscopic exploration.

Diagnosis of tularaemia

In any infection of the head and neck area with associated lymphadenopathy, the clinician should bear in mind not only common agents but also rare pathogens such as *F tularensis*. The incubation period of tularaemia is two to six days on average, with a range of one to 20 days. An excessive, unilateral lymphadenopathy is typical. The clinician should be especially alerted by the presence of multiple, suppurative lymph nodes in a patient of good general condition, along with slow clinical progression, similar to cervical tuberculosis. In contrast to invasive bacterial diseases, tularaemia is generally not associated with dramatic changes in blood chemistry (e.g. changes in CRP and white blood cell count).

The mainstay of tularaemia diagnosis is detection of antibodies against *F tularensis* by microagglutination assay or enzyme-linked immunosorbent assay. The antibody response appears at the end of the second week after onset of disease. Upon clinical recovery, titres decline slowly, but antibodies may persist for several years. For diagnostic purposes, preferably two serum samples are taken, one in the acute phase and another three weeks later. A four-fold increase in titre will confirm the diagnosis. However, patients may seek attention after their

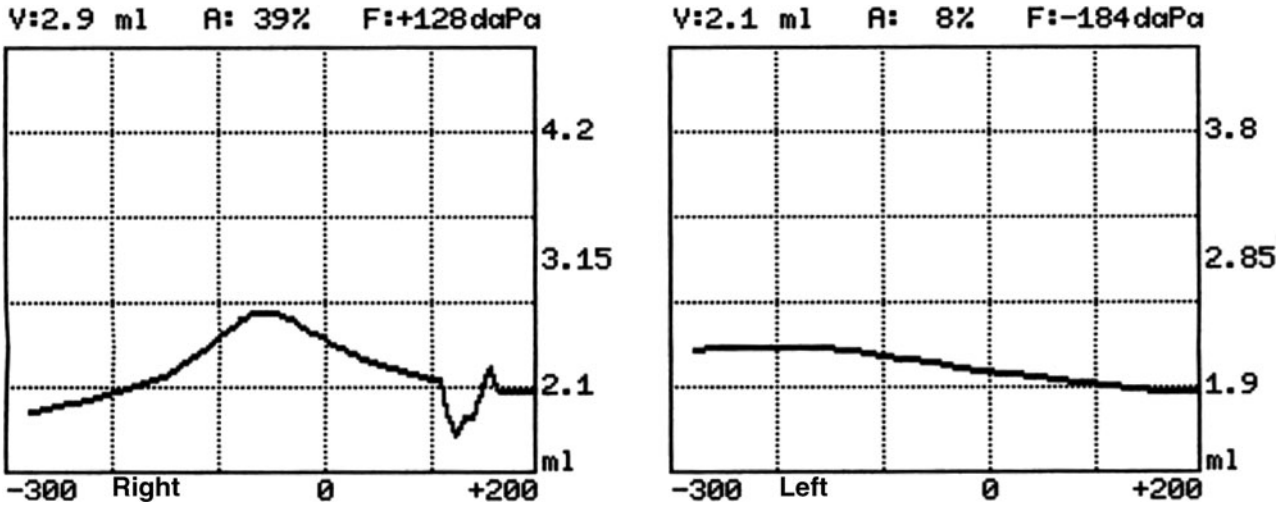

FIG. 4
Tympanogram showing a type B pattern in the left ear, suggesting tympanic effusion.

https://doi.org/10.1017/S0022215109004757 Published online by Cambridge University Press

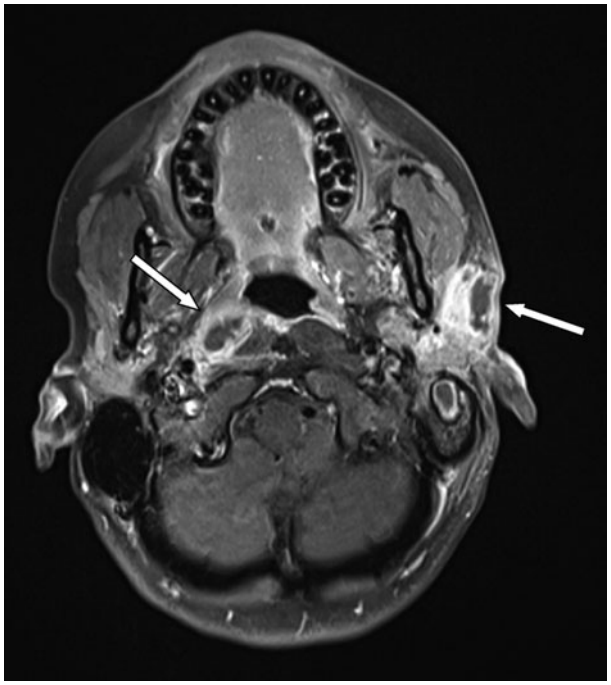

FIG. 5

Axial, T1-weighted, contrast-enhanced magnetic resonance imaging scan, showing suppurative lesions in the left preauricular and right retropharyngeal regions (arrows).

antibody level has peaked. A single sample showing a titre of >160 is regarded as confirmatory. In addition, a subsequent sample taken several months later showing a four-fold reduction of antibody titre can also be taken as confirmatory.

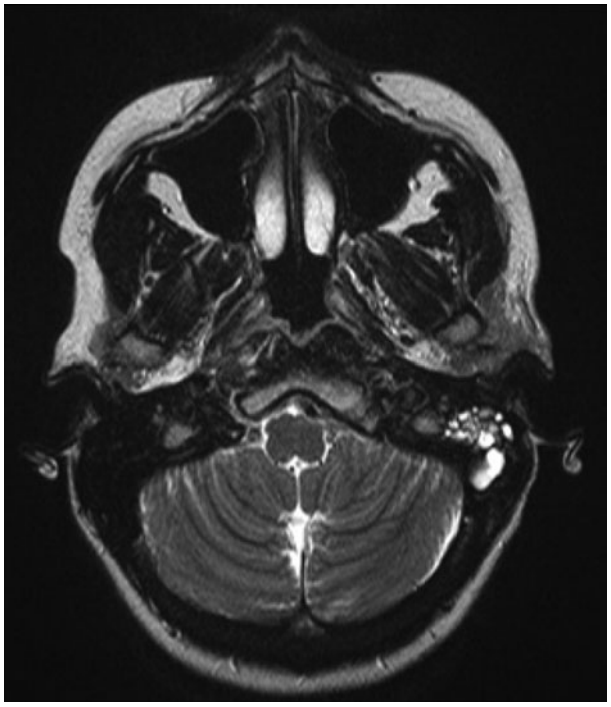

FIG. 6

Axial, T2-weighted magnetic resonance imaging scan showing left mastoid effusion.

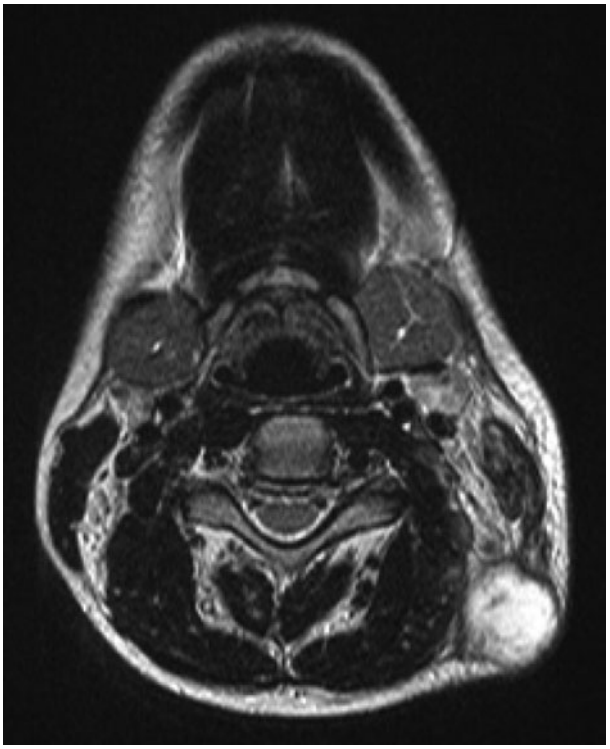

FIG. 7

Axial, T2-weighted magnetic resonance imaging scan taken four weeks after presentation, showing left laterocervical abscess formation.

Since *F tularensis* is fastidious and relatively slow-growing, cultures are often unsuccessful. When sample tissue or aspirate is available, polymerase chain reaction should also be performed, since it is the more powerful diagnostic tool, with a sensitivity of approximately 80 per cent and a rapid processing time.[13]

Discussion

Tularaemia is a very rare disease in central Europe. The oropharyngeal form accounts for only 1–4 per cent of all tularaemia cases and is usually characterised by pharyngitis and lymphadenopathy. Here, we present a unique case with acute otitis media as the primary manifestation and long-lasting conductive hearing loss as a consequence. A medical medline database search yielded only one article on tularaemia affecting the middle ear; a 2002 report of a 10-year-old Finnish boy with tularaemia of the middle ear.[7]

Due to its rarity and variable presentation, the diagnosis of tularaemia is difficult and therefore often delayed. Many differential diagnoses need to be considered for symptoms such as fever, sore throat and lymphadenopathy. These include mononucleosis, acute bacterial tonsillitis, bartonellosis, tuberculosis and others. To complicate matters further, our patient spent the first 15 days after clinical manifestation of the disease abroad, and was referred to a hospital only on day 35 of the clinical course. Thus, it took six weeks for our patient to be correctly diagnosed and commenced on specific antibiotic treatment. Tularaemia may well be generally underdiagnosed, because the ample use of antibiotics in patients with the above mentioned symptoms may conceal the typical disease course in many cases.

During our patient's long period of hospitalisation, she was in excellent general condition, which may suggest

https://doi.org/10.1017/S0022215109004757 Published online by Cambridge University Press

that infection with *F tularensis* is often not detrimental. Nevertheless, timely commencement of adequate therapy is important to prevent serious complications. Tularaemia is a potentially fatal disease with an estimated mortality rate of between less than 1 and 14 per cent, depending on the subspecies involved.[14] In the pre-antibiotic era, as many as 33 per cent of infected patients died.[15] Without appropriate treatment, our patient's inflammation of cervical soft tissue could have developed into life-threatening mediastinitis. However, despite intensive, specific antibiotic therapy, there was no satisfactory resolution of our patient's cervical swelling, such that surgical treatment of the multilocular abscesses was necessary.

In order to clarify the possible route of transmission in our patient, we questioned her thoroughly about her activities before the onset of disease. The first symptoms occurred on 31 July. Between 1 July and 15 August, the patient had stayed in Lyon, France. There, she had been exposed to mosquito bites, and had also had contact with both a domestic rabbit and a cat known to hunt rats. Neither the rabbit, the cat nor any other individuals in contact with these two animals had shown any symptoms suggesting infection. The patient was not aware of any tick bites or erythema. Poorly cooked wild animal meat was excluded as a source of infection. However, one week prior to the first manifestation of tularaemia, the patient had been actively involved in canyoning in the east of France. Consequently, a possible route of infection may have been accidental ingestion of contaminated water during this outdoor activity. Three other persons who also took part in the water sports activities were in good health, but serological investigations excluding subclinical infection were not performed. Considering all the facts, the patient's oropharyngeal contact with water seems to have been the most likely route of infection, but a definitive statement cannot be made.

- **Tularaemia is a rare zoonosis caused by the Gram-negative coccobacillus *Francisella tularensis***
- **Following an animal bite (from rodents or cats) or transmission by ticks or mosquitoes, the ulceroglandular form of the disease occurs, with skin lesions, fever and lymphadenopathy**
- **This paper describes an extremely rare case of otitis media due to *F tularensis*, complicated by multiple suppurative cervical lesions and a lasting conductive hearing loss**
- **Otitis media unresponsive to conventional therapy and accompanied by unusually pronounced lymphadenopathy should prompt the clinician to consider tularaemia as a differential diagnosis, in order to initiate timely, specific therapy**

According to most authors, the aminoglycosides streptomycin and gentamicin are the drugs of choice for tularaemia treatment.[16,17,18] One of the most important side effects of these antibiotics, however, is ototoxicity. Since our patient was a music teacher, we were reluctant to risk damaging her inner ear. Therefore, we started treating her with ciprofloxacin, which has recently been reported as suitable for tularaemia.[19,20] However, neither ciprofloxacin nor gentamicin, which was added later, could sufficiently relieve the patient's symptoms, probably because antibiotic treatment was initiated too late.[21] Only after open surgical incision and drainage did the lesions start to resolve. They continued to secrete small amounts of serous fluid for several months before healing spontaneously. Surgical incision and drainage is not always necessary in oropharyngeal tularaemia. It seems to be required when specific treatment is delayed and when manifest suppuration has developed. During an outbreak of oropharyngeal tularaemia in Turkey, 66 per cent of patients required lymph node excision or drainage. In this patient group, the average delay before initiation of an appropriate antibiotic (streptomycin) was eight weeks.[22]

Conclusion

Tularaemia should be taken into consideration in patients presenting with prolonged otitis media associated with lymphadenopathy which is unresponsive to antibiotic treatment, especially when common pathogens cannot be found.

Acknowledgement

The first author was supported by a scholarship of the Programm zur Förderung von Forschung und Lehre of the University of Munich.

References

1 Ellis J, Oyston PC, Green M, Titball RW. Tularemia. *Clin Microbiol Rev* 2002;**15**:631–46
2 Schmid GP, Kornblatt AN, Connors CA, Patton C, Carney J, Hobbs J *et al*. Clinically mild tularemia associated with tick-borne *Francisella tularensis*. *J Infect Dis* 1983;**148**: 63–7
3 Robert-Koch-Institut. Tularemia – Epidemiology in Germany [in German]. *Epidemiol Bull* 2007/Nr.7
4 Capellan J, Fong IW. Tularemia from a cat bite: case report and review of feline-associated tularaemia. *Clin Infect Dis* 1993;**16**:472–4
5 Gill V, Cunha BA. Tularemia pneumonia. *Semin Respir Infect* 1997;**12**:61–7
6 Peter R, Banyai T. Erythema nodosum revealing oculoglandular tularemia. *Dermatology* 2001;**202**:79–80
7 Luotonen L, Tapiainen T, Kallioinen M, Luotonen J. Tularemia of the middle ear. *Pediatr Infect Dis J* 2002;**21**: 264–5
8 Splettstoesser WD, Matz-Rensing K, Seibold E, Tomaso H, Al Dahouk S, Grunow R *et al*. Re-emergence of *Francisella tularensis* in Germany: fatal tularaemia in a colony of semi-free-living marmosets (*Callithrix jacchus*). *Epidemiol Infect* 2007;**135**:1256–65
9 Fujita O, Tatsumi M, Tanabayashi K, Yamada A. Development of a real-time PCR assay for detection and quantification of *Francisella tularensis*. *Jpn J Infect Dis* 2006;**59**: 46–51
10 Bystrom M, Bocher S, Magnusson A, Prag J, Johansson A. Tularaemia in Denmark: identification of a *Francisella tularensis* subsp. *holarctica* strain by real-time PCR and high-resolution typing by multiple-locus variable-number tandem repeat analysis. *J Clin Microbiol* 2005;**43**:5355–8
11 Broekhuijsen M, Larsson P, Johansson A, Bystrom M, Eriksson U, Larsson E *et al*. Genome-wide DNA microarray analysis of *Francisella tularensis* strains demonstrates extensive genetic conservation within the species but identifies regions that are unique to the highly virulent *F. tularensis* subsp. *tularensis. J Clin Microbiol* 2003;**41**:2924–31
12 Schmitt P, Splettstoesser W, Porsch-Ozcurumez M, Finke EJ, Grunow R. A novel screening ELISA and a confirmatory Western blot useful for diagnosis and epidemiological studies of tularemia. *Epidemiol Infect* 2005;**133**:759–66
13 Johansson A, Berglund L, Eriksson U, Goransson I, Wollin R, Forsman M *et al*. Comparative analysis of PCR versus culture for diagnosis of ulceroglandular tularemia. *J Clin Microbiol* 2000;**38**:22–6
14 Staples JE, Kubota KA, Chalcraft LG, Mead PS, Petersen JM. Epidemiologic and molecular analysis of human tularemia, United States, 1964–2004. *Emerg Infect Dis* 2006;**12**: 1113–18

15 Wills PI, Gedosh EA, Smith F, Nichols DR. Head and neck manifestations of tularemia. *Laryngoscope* 1982;**92**:770–3
16 Everett ED. Clinical manifestations, diagnosis, and treatment of tularaemia. 2007. Available via uptodate.com, accessed June 24th 2008
17 Enderlin G, Morales L, Jacobs RF, Cross JT. Streptomycin and alternative agents for the treatment of tularemia: review of the literature. *Clin Infect Dis* 1994;**19**:42
18 Tärnvik A, Chu MC. New approaches to diagnosis and therapy of tularemia. *Ann N Y Acad Sci* 2007;**1105**: 378–404
19 Johansson A, Berglund L, Gothefors L, Sjöstedt A, Tärnvik A. Ciprofloxacin for treatment of tularemia in children. *Pediatr Infect Dis J* 2000;**19**:449–53
20 Limaye AP, Hooper CJ. Treatment of tularemia with fluoroquinolones: two cases and review. *Clin Inf Dis* 1999;**29**: 922–4
21 Tarnvik A, Berglund L. Tularemia. *Eur Respir J* 2003;**21**: 361–73
22 Celebi G, Baruönü F, Ayoğlu F, Cinar F, Karadenizli A, Uğur 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

Address for correspondence:
Dr Robert Gürkov,
Department of Otorhinolaryngoloy Head and Neck Surgery,
University of Munich,
Marchioninistrasse 15,
81377 Munich, Germany.

Fax: +49 89 7095 6869
E-mail: robert.guerkov@med.uni-muenchen.de

Dr R Gürkov takes responsibility for the integrity of the content of the paper.
Competing interests: None declared