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BRIEF REPORT

Treatment of cervical adenopathies secondary to oropharyngeal tularaemia. Our experience in 8 patients

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KEYWORDS
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Abstract
Tularaemia is an uncommon zoonosis in our country. During the outbreak in 2007, there was a notably high incidence of the oropharyngeal form. We report our experience in 8 patients with oropharyngeal tularaemia with cervical adenopathies.
The mean age was 45 years (11-76), with 5 males. All suffered oropharyngeal pain, fever, and asthenia. The time elapsed between the onset of symptoms and attending our clinic varied from 8 to 60 days. Mean duration of oropharyngeal symptoms was 11.7 days, and adenopathies appeared in the first 3 days. Resolution of adenopathies occurred at 2 to 3.5 months. Three cases needed surgical drainage and 2 fistulized spontaneously. Seven patients were treated with ciprofloxacin and 1 with erythromycin.
A correct and precocious antibiotic therapy, and sometimes surgical drainage, could accelerate the healing process.

PALABRAS CLAVE
Tularemia;
Adenopatía cervical;
Ciprofloxacino;
Drenaje quirúrgico;
Fístula

Tratamiento de adenopatías cervicales secundarias a tularemia orofaríngea. Nuestra experiencia en 8 pacientes

Resumen
La tularemia es una zoonosis infrecuente en España. En el brote iniciado en 2007, destaca la elevada incidencia de su forma orofaríngea. Describimos nuestra experiencia en el tratamiento de 8 pacientes con adenopatías cervicales por tularemia orofaríngea.

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El estudio se realizó en 5 varones y 3 mujeres, con una edad media de 45,3 (rango: 11-76) años. En todos aparecieron dolor orofaríngeo, fiebre y astenia. El tiempo desde el comienzo de los síntomas hasta la consulta a nuestro servicio osciló entre 8 y 60 días. La duración media de los síntomas orofaríngeos fue de 11,7 días, y las adenopatías aparecieron en los primeros 3 días. La resolución de estas adenopatías ocurrió al cabo de 2-3,5 meses. Tres casos precisaron el drenaje quirúrgico y 2, fistulizaron de forma espontánea. Se trató a 7 pacientes con ciprofloxacino y a uno con eritromicina.
Un correcto tratamiento antibiótico temprano, y en algunos casos el drenaje quirúrgico, podrían acelerar la curación.

Introduction

Tularaemia is a zoonosis caused by *Francisella tularensis*, a Gram-negative cocobacillus with 3 possible biovars: *a) tularensis* (also known as *nearctic* or type A), typical of North America; *b) palearctica* (*holarctic* or type B), common in Eurasia and less virulent than the previous one; and *c) novicida*, which has been described as a human pathogen on very rare occasions.[1] Its main reservoir lies in small rodents and lagomorphs in the northern hemisphere, although it can also be isolated in many other animal species.[1,2]

McCoy and Chapin first described it in the region of Tulare (California) in 1912.[3] On the Iberian Peninsula, it was a practically unknown entity until 1997, when an epidemic outbreak was recorded in the Region of Castilla y León.[4] Subsequently, the number of cases diminished till its almost total disappearance and it re-emerged in 2007 in the form of a new outbreak.[5]

It presents 6 possible clinical forms: ulceroglandular or ulceroganglionar, glandular or ganglionar, pneumonia, typhoid, oculoglandular, and oropharyngeal. The form of involvement essentially depends on the germ's access route: the inhalation of contaminated aerosols constrains pneumonia-like or oropharyngeal forms; the consumption of polluted water or insufficiently cooked meat leas to typhoid or oropharyngeal forms; and stings by arthropods and direct contact through abrasions on the skin and mucosae cause ganglionar, ulceroganglionar, and oculoglandular forms.[1]

In the outbreak that started in 2007, the most outstanding form was the high number of cases of oropharyngeal tularaemia (OT). This contrasts with its scant appearance in the outbreak in Castilla y León between 1997 and 1998 and in the European literature. Relative incidences are estimated at less than 1% of the total number of patients with this disease in Scandinavian countries.[4,6,7] Special mention must be made of the situation in Turkey, where, on the other hand, the predominant form is oropharyngeal.[8] Our goal is to describe our experience in the treatment of cervical adenopathies caused by OT.

Methods

Between June 2007, and February 2008, a total of 497 cases of tularaemia were declared in Spain, of which 276 corresponded to our province of Palencia. We have selected 8 of these cases, with OT and cervical adenopathies, treated at the Otorhinolaryngological Department of the Palencia Hospital Complex. The inclusion criteria established were: diagnosis of tularaemia, existence of pharyngitis and/or amygdalitis for at least one week, and the onset of palpable cervical adenopathies. For the diagnosis of tularaemia, we have followed the criteria of the US Center for Disease Control. This centre defines confirmed tularaemia as the existence of a compatible clinical presentation together with the presence of confirming laboratory criteria: seroconversion (four-fold elevation in titres of antibodies against *F tularensis*), raised titre of immunoglobulin M against *F tularensis*, direct visualization of the agent, or positive polymerase chain reaction in biological samples. Likely tularaemia would be the existence of compatible clinical presentation plus presumptive laboratory criteria: elevated titre of antibodies against *F tularensis* (≥1/160) or a positive ELISA test.[4]

Retrospectively, information was recorded for the patients selected with regard to their age, gender, the time elapsed from the onset of the symptoms until their first contact with our department, the duration of the oropharyngeal symptoms (pharyngitis and/or amygdalitis), the time elapsed from the onset of the symptoms until the appearance of the adenopathies, the size and location of the adenopathies, their general symptoms, antibiotic treatment prior to arrival at our department, the antibody titres, specific antibiotic treatment after arrival at our department, and the course of the adenopathies (resolution with antibiotics, spontaneous fistulization, or surgical drainage when appropriate antibiotic treatment did not lead to an evident improvement). Titration was effected using the microagglutination technique.

Results

The study was carried out on 5 males and 3 females, with a mean age of 45.3 years (range, 11-76) (Table 1). In the initial phase, oropharyngeal pain, high fever, and asthenia were seen in all 8 cases, cephalea in 4, pain in the upper limbs in 1, and pain in the lower limbs in 1. The time elapsed between the start of their symptoms and the first visit to our clinic varied between 8 days and 2 months (mean, 32.2 days). No patient had direct contact with rodents or

Table 1 Characteristics of the patients studied on arrival at the clinic

Case	Age, y	Gender	TCon	Prior antibiotics	Systemic symptoms	TAnt
1	41	M	60	AM, CLA	Fever, asthenia, UL pain	1/320 1/640
2	38	F	45	AM-C, CEF, CLI	Fever, asthenia, LL pain	1/5120
3	11	F	30	AM-C	Fever, asthenia	1/5120
4	45	M	18	AM-C, CLI, GEN	Fever, asthenia	1/640
5	60	M	8	AM	Fever, asthenia	1/160
6	32	M	37	ER, CLA	Fever, asthenia	1/5120
7	76	M	30	CP	Fever, Asthenia	1/360 1/1.280
8	60	F	30	–	Fever, asthenia	1/320 1/320

AM indicates amoxicillin; AM-C,: amoxiclavulanic acid; CEF, cefuroxime; CLA, clarithromycin; CLI, clindamycin; CP,: ciprofloxacin; ER, erythromycin; F, female; GEN, gentamycin; LL, lower limbs; M, Male; TAnt, titre for antibodies against *Francisella tularensis* (in some cases, first and second titres); TCon, time from the onset of symptoms until first consultation, in days; UL, upper limbs.

Table 2 Specific antibiotic treatment, course of the oropharyngeal clinical presentation, and characteristics and course of the adenopathies

Case	TOro	TAde	Size of adenopathies	Location of adenopathies	Antibiotic treatment	Course of adenopathies	TRes
1	15	2	4×3 cm	Bilateral	CP 3 weeks	Drainage	3
2	10	1	4×5 cm	Unilateral	CP 4 weeks	Drainage	3
3	8	2	4×3.2 cm	Unilateral	ER 4 weeks	Spontaneous resolution	2
4	18	2	5.3×3 cm	Unilateral	CP 3 weeks	Spontaneous resolution	3.5
5	8	2	6×5.5 cm	Unilateral	CP 2 weeks	Fistulization	3
6	20	2	5×4.5 cm	Unilateral	CP 2 weeks	Spontaneous resolution	2
7	7	3	4.4×2.5 cm	Unilateral	CP 2 weeks	Fistulization	2.5
8	7	2	3.5×3 cm	Unilateral	CP 5 weeks	Drainage	2

CP indicates ciprofloxacin; ER, erythromycin; TAde, time from the start of symptoms until the appearance of the cervical adenopathies, in days; TOro, total duration oropharyngeal symptoms, in days; TRes, total time from the appearance of the adenopathies until their resolution, in months.

Figure 1 Bilateral adenopathies.

lagomorphs, and the only exposure factor observed in all of them was spending time in the countryside.

The mean duration of the oropharyngeal symptoms was 11.6 days (range, 7-20) (Table 2), and adenopathies generally appeared between the 1st and 3rd day after the start of clinical symptoms, causing pain in all cases (Figure 1). Five patients (62.5%) developed subsequent reddening of the skin and fluctuation of the adenopathies.

After the diagnosis of tularaemia was established, treatment was begun with ciprofloxacin in all patients, except for one 11-year-old girl, in whom quinolone was replaced by erythromycin to avoid damage to her growing cartilage. The duration of the antibiotic treatment varied between 2 and 5 weeks. The definitive resolution of their adenopathies occurred after 2-3.5 months (mean, 2.6 months). For this to happen, 3 of the cases (37.5%) required surgical drainage due to a poor or slow response to the antibiotic treatment given (Figure 2), and spontaneous fistulization was seen in 2 cases (25%) (Figure 3).

Figure 2 Suppuration after surgical drainage.

Figure 3 Developed form of adenopathy.

Discussion

In the 1997-1998 outbreak of tularaemia in the Spanish Region of Castilla y León, the predominant forms were ulceroglandular and ganglionar, and a clear association was found between the development of the disease and the manipulation of contaminated hares by hunters and their relatives. Over this period, the percentage of OT varied between 1.4% described by Pérez-Castrillón et al[9] in Valladolid (2 patients out of a total of 142 cases of tularaemia) and 11.36% (5 of 44) in our series in Palencia.[4,6] In the 2007-2008 outbreak, however, the percentage of pneumonia-like, typhoid and oropharyngeal forms was higher and, in most cases, a history of walking in the countryside, carrying out agricultural activities or drinking contaminated water was observed. We believe that the germs reached the oropharyngeal mucosa of our patients by being breathed in and this triggered, almost simultaneously, the cervical adenopathies in addition to the systemic symptoms, amygdalitis, and pharyngitis. Cervical adenopathies are initially hard and painful, with a subsequent tendency to grow in size, fluctuate, reddening the skin surrounding them and, finally, they spontaneously fistulize. In the cases reported here, we observed that the empirical initial use of antibiotics not targeting tularaemia (generally betalactamics) brought about a speedy resolution of the pharyngoamygdaline problems but could not slow up the progression of the adenopathies.

We have confirmed that there is a considerable delay between the onset of symptoms and the date on which patients come to our clinic. Previous studies coincide in the need to institute treatment early in order to avoid complications.[8,10] Nonetheless, the scant incidence, together with the difficulties involved in their diagnosis (level 3 biosafety measures are recommended for laboratory personnel due to the high risk contagion during sample cultures and, on the other hand, it is common for the antibodies against *F tularensis* to be still undetectable in the first 7-10 days), have probably contributed to this delay.[11] Perhaps the generalized use of polymerase chain reaction, added to the greater awareness of the condition, might in the near future shorten the time for diagnosis, as has happened in Scandinavian regions, where there have been repeated outbreaks.[7,12]

We treated our adult patients with ciprofloxacin, at a dose of 1500 mg/day, for a minimum of 14 days. The progression of the symptoms determined the need to extend treatment. In minors, due to the toxicity of quinolones and the favourable sensitivity of the strain of *F tularensis* we are dealing with, erythromycin was used. In all cases, the progression of the adenopathies was slowed with these antibiotics and they were even resolved in 3 patients; their persistence in another 3 required surgical drainage, without resection being necessary.

Thus, we are facing a new entity that should be taken into account in our setting. In our experience, cervical adenopathies due to OT are long-lasting processes that require appropriate treatment and follow-up in order to obtain a total cure in 100%of cases. When facing any clinical suspicion, the correct antibiotic treatment should be started at an early stage, even without serological confirmation, so as to avoid complications and sequelae. In some cases, the process can be shortened by surgical draining.

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