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AN UNCOMMON CASE OF TULARAEMIA IN PORTUGAL AFTER AN ARTHROPOD BITE

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ABSTRACT

Tularaemia is a rare zoonosis caused by *Francisella tularensis*, with only a few reported cases in Western Europe and only 4 notified in Portugal between 2014 and 2021. We describe an imported case diagnosed in Portugal in 2023. A 40-year-old female developed a painful left inguinal lymphadenopathy after an arthropod bite in England. Despite initial treatment with doxycycline, symptoms persisted with systemic manifestations and progressive lymphadenopathy. Serology tests confirmed *F. tularensis* infection. The patient required prolonged follow up and antibiotic adjustment, showing gradual clinical improvement. This case highlights the diagnostic challenges of tularaemia and the importance of thorough physical examination and epidemiological history.

KEYWORDS

Tularaemia, Portugal, *Francisella tularensis*, zoonosis

LEARNING POINTS

- Diagnosing and differentiating zoonosis presents a challenge, since it is important to remember even the rarer and imported ones, such as tularaemia.
- Once the diagnosis is made, the clinical condition and treatment of the patient may not evolve as expected, being important for the clinician to adjust to new findings.

INTRODUCTION

Tularaemia is a zoonosis caused by *Francisella tularensis*, a gram-negative non-motile intracellular bacterium[1-3]. This disease can be transmitted to humans by arthropod bites, direct contact with infected animals (such as rodents, hares and rabbits), infected animal tissues or fluids, ingestion of contaminated water or food, or inhalation of infective aerosols[1-3].

Tularaemia has been reported mostly in the northern hemisphere. In Europe, cases are reported each year from most countries in eastern and central Europe, with only a few reported cases in continental western Europe[3,4].

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According to the European Union One Health Zoonoses report, between 2017 to 2023, there has been a significant increasing trend in tularaemia cases, with 1185 confirmed cases in 2023, and infections peaking in summer months[4-6]. There are four types of *F. tularensis* subspecies[1-3]. *F. tularensis* subspecies tularensis (type A strains) and holarctica (type B strains) are the main cause of tularaemia in the world, with type B being responsible for tularaemia in Europe[2].

In 2007 a study showed the first direct evidence of *F. tularensis* in Portugal, by analysing human blood samples through molecular methods[7]. Tularaemia became a notifiable communicable disease in 2003, in line with epidemiological surveillance in Europe[1]. The first human case of tularaemia in Portugal (probably imported), was published in 2018, and the first report of autochthonous tularaemia in Portugal was published in 2022[1]. According to the European Centre for Disease Prevention and Control, 4 cases of tularaemia in humans were notified in Portugal between 2017-2022[4-6]. We describe an imported case of tularaemia in Portugal from 2023 and illustrate how this rare disease poses diagnostic challenges.

CASE DESCRIPTION

This case was reported in 2023 in Lisbon, Portugal. A 40-year-old female, native from Poland, but living in Portugal for 3 months, had a medical history of dysrhythmia treated with bisoprolol 2.5 mg once per day. She reported recent trips to Poland, South Africa and England. She reported an arthropod bite in her lower back that occurred when she was visiting the London area, in England. After 13 days, a painful inguinal mass in the left side appeared suggesting lymphadenopathy, alongside a red swollen area in the left lumbar region compatible with an arthropod bite *(Fig. 1)*.

She went to the emergency department, where a complete work-up was done: blood tests revealed a haemoglobin of 13.7 g/dl, 6,900 leucocytes/µl, with 40.7% of neutrophils (2,808/µl) and 40.7% lymphocytes (2,808/µl), with an increased C-reactive protein (5.2 mg/dl); erythrocyte sedimentation rate of 17 mm/hour; and negative serology for Lyme disease (no immunoglobulin M [IgM] and immunoglobulin G [IgG] antibodies to *Borrelia burgdorferi*), while serology for *Rickettsia conorii* showed positive IgG and negative IgM antibodies, revealing a previous exposure. Two days after the first admission, the painful lymphadenopathy persisted, and the patient returned to the emergency department. She underwent a computed tomography scan of the abdomen and pelvis with no pathological findings, and a new blood work-up with normal values. The red swollen lesion in the left lumbar area evolved developing a crust *(Fig. 2)*.

Assuming a possible diagnosis of zoonosis, she was discharged from the emergency department medicated with doxycycline 100 mg 12 to 12 hours for 8 days.

After completing the treatment, she returned to the emergency department, complaining of symptoms persistence accompanied by night sweats, feeling feverish and dry cough. On physical examination bilateral lymphadenopathy in the inguinal, cervical and axillary areas was noted. The laboratory results showed haemoglobin 13.2 g/dl, without leucocytosis (7,400 leucocytes/µl, of which 3,790 neutrophils/µl and 3,390 lymphocytes/µl), with C-reactive protein of 1.1 mg/dl. Additional exams were done: fourth generation testing for human immunodeficiency virus (HIV) (p24 antigen and HIV-1/2 antibodies) was negative; serologic testing for hepatitis B showed immunization (negative hepatitis B surface (HBs) antigen, negative hepatitis B core antibody and positive HBs antibody) and was negative for hepatitis C virus (HCV) (HCV antibody negative). An abdominal ultrasound was performed, excluding hepatosplenomegaly, and revealing reactive lymph nodes in the inguinal area.

After 21 days from the onset of symptoms, laboratory results from the first visit to the emergency department revealed a positive IgM antibody for *F. tularensis* (titter levels were not provided by the laboratory). The patient was treated with doxycycline for 29 days, but showed no clinical improvement, leading to the decision to switch antibiotic therapy to ciprofloxacin 500 mg 12 to 12 hours. However, due to neurological symptoms with generalized tremor, tinnitus



Figure 1. *Red swollen area in the left lumbar region.*



Figure 2. *Red swollen lesion in the left lumbar area evolved with a crust.*

and malaise, she did not tolerate ciprofloxacin, ending up doing only 2 days of this antibiotic. The patient had follow-up appointments in Infectious Diseases and Internal Medicine, where a second IgM antibody test for *F. tularensis* was positive (titter levels not available), and showed progressive symptomatic improvement, with symptom resolution. Two and a half months later, the patient developed epigastric abdominal pain and a cervical tumefaction. She was treated with gentamicin for 3 days, with gradual improve, returning to her usual life.

DISCUSSION

Of the four subspecies of *F. tularensis*, the subspecies tularensis is found exclusively in North America, is more virulent and is associated with most infections and deaths in humans, while the subspecies holartica is the most common in Europe[2,3]. According to the European Centre for Disease Prevention and Control, between 2017-2019 there was only one case of tularaemia reported in the United Kingdom (UK)[4-6]. A review of the literature found one case report describing an infection with F. *tularensis holartica* in a patient from the UK in 2023[8]. However, the origin of this infection was not clearly understood: the patient had visited Portugal previously, but the timeline for acquisition in this country made it an unlikely origin; infection through his companion animals was ruled out too, with the animals testing negative; inoculation in the UK was not ruled out, considering the possibility of an unidentified environmental reservoir, with possible transmission by a biting arthropod[8]. In our case, the medical history, with the arthropod bite noticed in England (prior to the trip to Portugal), and the timing of inoculation, suggests probable infection in the UK. Therefore, our case would be the third case report of tularaemia related to this country, suggesting possible transmission with an unidentified reservoir in UK. It is possible to theorize that rising numbers in tularaemia cases may be related to ecological and behavioural factors, alongside improved clinician awareness leading to a more accurate diagnosis. Under these circumstances, the most likely subspecies causing infection would be *F. tularensis* holartica, which is the most common in Europe[2,8].

Tularaemia is transmitted to humans through handling and contact with infected animals, tissues or fluids, vector bites, consumption of contaminated food or water, and aerosol inhalation. The main wild animal carriers of this disease are leporids and a variety of rodents. In domestic animals, tularaemia occurs in sheep, cats, rabbits, dogs, pigs and horses. Due to the main carriers, tularaemia is also known as rabbit fever. Arthropod vectors such as ticks, biting flies, and mosquitoes are also an important transmission route of tularaemia to humans[1-3]. In this case the most likely transmission pathway was infection by a vector bite, corroborated by the skin lesion and a biting sensation that the patient previously had.

The incubation period is usually 3 to 5 days but can be extended up to 14 days. The symptoms include fever with malaise, chills and headache. There are six forms of clinical tularaemia: ulceroglandular, glandular, pneumonic, oropharyngeal, oculoglandular, and systemic. The site and route of infection determine the clinical form of the disease[1-3]. The oropharyngeal form is typical when there is ingestion of the bacteria. Usually, infection by direct contact or a vector bite results in ulceroglandular tularaemia. If the skin lesion is not detected it is considered glandular tularaemia. The oculoglandular form is most common when contaminated hands or fluids of a contaminated animal enters in contact with conjunctiva. Pneumonic tularaemia occurs when there is inhalation of infectious aerosols. The systemic form appears with infection of *F. tularensis* that spreads through the bloodstream and is most associated with a pneumonic and typhoidal presentation[2].

In our case the symptoms started 13 days after the bite and included painful lymphadenopathy and an inoculation lumbar lesion, appearing to be an ulceroglandular form of tularaemia.

There is clinical suspicion when a patient has fever, lymphadenopathy and contact with rodent animals or a vector bite. The diagnosis relies on positive serology with a compatible clinical and epidemiological context. Regarding laboratory tests, the microscopic agglutination test (MAT) or enzyme-linked immunosorbent assay (ELISA) can detect serum antibodies for *F. tularensis*. For the diagnosis of tularaemia to be confirmed, it is necessary to have a four-fold increase in anti-*Francisella* serum antibody titter, within 2–4 weeks. It is noteworthy that *Salmonella*, *Brucella*, *Legionella*, and *Yersinia spp.* may cause false positive results with serological cross-reactivity[2].

In our case we cannot confirm a four-fold rise in the antibody titter, due to absence of this information provided by the laboratory. However, two positive IgM tests from different hospitals, a suggestive history and clinical expression, with the remaining zoonosis testing negative, supports and strengthens our diagnosis of tularaemia.

Antibiotic therapy plays an important role to prevent complications, shorten the recovery period and decrease mortality. The choice of antibiotics needs to be personalized, but aminoglycosides, tetracyclines, quinolones, and chloramphenicol are the most used[1-3]. Doxycycline can be taken for up to 21 days, fluoroquinolone for up to 14 days, and aminoglycosides for up to 10 days, to decrease the relapse rates. The usual regimens for mild infections are ciprofloxacin 500 mg 12 to 12 hours or doxycycline 100 mg 12 to 12 hours, for 14 days[2,3].

In this case, the patient was given doxycycline for 29 days because symptoms persisted for a long time, with afterwards switch to ciprofloxacin, due to lack of improvement and a confirmed diagnosis of tularaemia. However, due to poor tolerability ciprofloxacin was discontinued. After a few months, with reappearing symptoms, the patient was treated with gentamicin for 3 days, with symptom resolution.

In conclusion, tularaemia is a rare zoonotic disease and challenging to diagnose. It may be hard to suspect, and

difficult to distinguish from other zoonoses, with physical examination playing an important role. Although it is rare, in a patient with persistent fever, despite empiric antibiotic therapy, lymphadenopathy and a history of arthropod bite or contact with animals, a diagnosis of tularaemia should be considered, especially given the increasing trend in tularaemia cases.

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