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Tularemia in British Columbia: A case report and review

Physicians, laboratory staff, and public health workers should be aware of this rare but potentially serious disease, which is contracted most commonly through animal or insect bites.

ABSTRACT: *Francisella tularensis*, the causative agent of tularemia, is endemic in British Columbia. Although uncommon, this zoonotic disease can cause life-threatening illness. A recent case led to a review of 16 other cases identified over a 15-year period through the integrated Public Health Information System and the BC Centre for Disease Control Public Health Microbiology and Reference Laboratory. All cases were likely acquired in rural areas. While skin lesions, often accompanied by regional lymphadenopathy, were the most common clinical presentation, two severe cases, one of septicemia and one of pulmonary infection, were noted. Most of the cases were identified by culture (56%), followed by serology (38%). In endemic areas, members of the public and individuals who handle wild animals should be aware of the disease. In addition, physicians, laboratory staff, and public health workers should be aware of the endemicity and infectiousness of *F. tularensis*, as well as its ability to cause serious illness and its potential for use in biological warfare.

Tularemia is a zoonotic disease caused by *Francisella tularenis*, which is endemic in British Columbia and other parts of Canada.[1,2] There are various clinical presentations, and diagnosis may be difficult. Because tularemia is a potentially serious and life-threatening disease that is treatable with appropriate antimicrobial agents, early clinical suspicion and appropriate diagnostic testing are required. Diagnosis is usually made by serologic testing or culture (or both); however, in most cases these methods are used only when there is clinical suspicion.

An unexpected case of tularemia diagnosed in rural BC in October 2006 led to a review of reported cases in the province to further define the clinical and public health importance of this infection. Although tularemia is rare, physicians, laboratory staff, and public health workers should be alert to the possibility of disease caused by *F. tularensis*.

Case report

A previously healthy 58-year-old male presented to a rural medical clinic in BC with an infected insect bite above his right knee. When he was examined, several lesions were found on his lower legs and an area of cellulitis was identified surrounding a lesion on his right knee. The patient was treated with an oral cephalosporin antibiotic. No cultures were performed at this time. The cellulitis resolved over the following weeks.

About 6 weeks later, the man returned to the same clinic, this time

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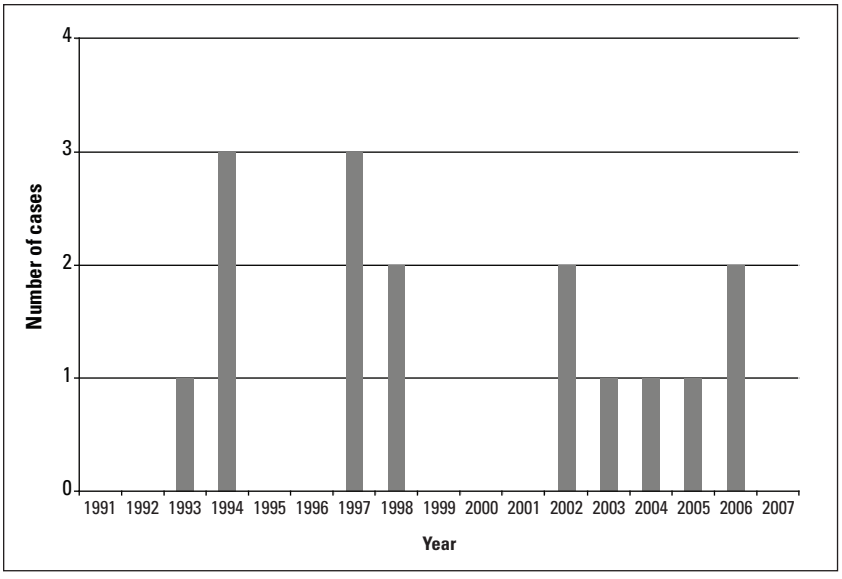

Figure 1. Tularemia infections diagnosed in BC, 1991–2007.

complaining of a painful lump in his right groin. On examination, the patient was found to be afebrile. A large, tender, fluctuant right inguinal lymph node was identified along with several adjacent lymph nodes that were mildly enlarged. A large amount of purulent material was aspirated from the inguinal lymph node. The patient was given a course of oral azithromycin, and the aspirated sample was sent to the BC Centre for Disease Control Public Health Microbiology and Reference Laboratory for investigation.

The conditions and organisms considered in the differential diagnosis included (in descending order) pyogenic bacterial abscess, *Bartonella henselae*, lymphogranuloma venereum (usually caused by *Chlamydia tracomatis*), mycobacterial infection, syphilis, reactive lymph node, *Yersinia pestis*, and *F. tularensis*. A Gram stain of the purulent material did not reveal any organisms, and there was no growth on culture after 5 days of incubation. Polymerase chain reaction (PCR) tests for *B. henselae* and *C. trachomatis* were both negative. Syphilis and mycobacterial infections were also excluded. A 16S rRNA test utilizing a broad-spectrum bacterial DNA target was performed on the aspirated sample. The amplified DNA product from the PCR was sequenced as per routine laboratory protocol[3] and identified as *F. tularensis*. Subsequently, serology for tularemia was performed and the patient's sample was found to be reactive, with a titre of 1:256. The patient was treated with a course of levofloxacin and recovered fully.

Cases of tularemia in BC, 1991–2007

To define the regional characteristics of this disease in BC, a retrospective review of all clinical information on cases of tularemia reported to the public health authorities was carried out. The laboratory-confirmed cases were identified through the electronic database of the provincial public health laboratory as well as the electronic database used by local public health officials for recording reportable diseases in BC, the integrated Public Health Information System (iPHIS). Although tularemia was not reportable in BC until 2002, some cases were reported to public health authorities before this date. For the purposes of this study, a positive laboratory-confirmed case refers to any positive result generated during the study period, regardless of methodology. However, this is contrary to the public health definition for a confirmed case: one where *F. tularensis* is isolated from an appropriate specimen type, where a fourfold increase in titre is demonstrated. Although a total of 16 patients (10 male) diagnosed with tularemia were identified from 1991 to 2007 (**Figure 1**), only 9 patients met the confirmed-case criteria and were followed up by public health, and the case described here had a single serum sample and a PR-positive result. Six cases had a single serum sample submitted that was positive. Without convalescent sera, these cases did not meet the public health criteria for a confirmed case. In these instances, no follow-up information was available.

The ages of the patients in this review ranged from 10 to 90 years, with a mean age of 53. The cases were identified through laboratory culture (56%), serology (38%), or by molecular testing (6%). All but one case (an out-of-province visitor) were residents of rural BC. Of the 10 cases that met the public health criteria for a confirmed case, the majority (87%) were residents of the Interior Health Authority and the Northern Health Authority (**Figure 2**). Of interest, half of these cases were known to be associated with either animal bites or insect bites, and all but two of the cases were diagnosed between May and October.

The most common type of tularemia in this series was ulceroglandular (64%), with seven cases where isolates were recovered from skin lesions on upper or lower extremities. Two cases were diagnosed by cultures from

conjunctival swabs and found to involve the rare oculoglandular type of infection. This is thought to occur when the conjunctiva is the initial site of infection, possibly as a result of patients transfering *F. tularensis* from their hands. In our series, we also noted one case where sputum cultures grew *F. tularensis*, and one where blood samples grew this bacterium. Based on the origin of the samples, it was determined that these were cases of the more severe forms of the disease, pneumonic and typhoidal tularemia respectively.

Outcome information was limited, but there was at least one death that was likely attributable to tularemia-related acute respiratory distress syndrome. Where follow-up information was available, it showed that many of the patients were treated with multiple ineffective courses of antibiotics before either a quinolone or gentamicin was prescribed.

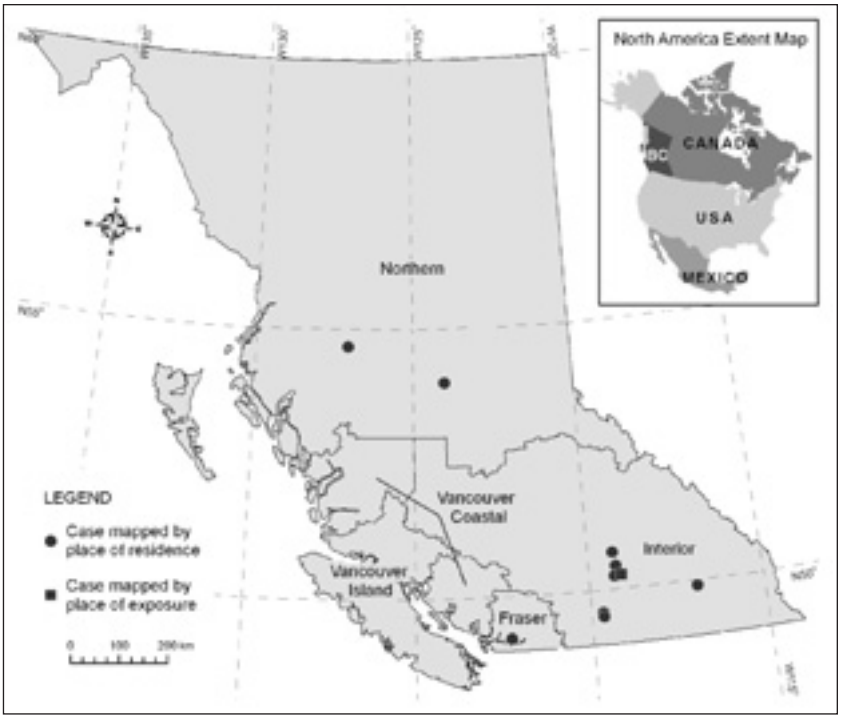

Figure 2. Tularemia infections in BC that met confirmed-case criteria, 1991–2007. BC health authority boundaries are delineated.

Microbiology and epidemiology

Francisella tularensis, the causative agent for tularemia, is a gram-negative coccobacillus identified in 1912 and named after Tulare County, California. This zoonotic agent was first described causing a "plague-like illness" in the area's ground squirrels,[4] although today the disease in humans is often referred to as rabbit or muskrat fever. Since 1912, four subspecies of *F. tularensis* have been described, each with a unique geographical distribution and biological characteristics.[5] Disease in humans is typically caused by two of these subspecies: the more virulent subspecies *tularensis* (also known as type A or subspecies *nearctica*), and the less virulent subspecies *holarctica* (also known as type B or subspecies *palearctica*), both of which are found throughout the United States and Canada.[5,6]

Humans are most commonly infected through insect bites or by handling infected animals.[3] Ticks are associated with approximately 90% of tularemia cases in the United States. *F. tularensis* has been isolated from ticks in BC, Ontario, and Saskatchewan.[1]

F. tularensis may also be contracted through inhalation, usually when cultures are manipulated in a laboratory setting.[7] This bacterium is highly infectious, with fewer than 10 organisms required to cause infection.[7] Aerosolized bacteria may also come from environmental sources such as hay contaminated by animal urine or feces or from decaying animal carcasses. Interestingly, one outbreak was traced to the inhalation of bacteria from an infected rabbit carcass aerosolized by a lawnmower.[8]

The reservoir of this zoonotic organism includes over 100 species of wild and domestic animals.[3] Direct contact with dead or diseased animals is one of the major causes of infection. The effect of the disease on infected animals varies. Rabbits, for example, often become severely ill, while most other hosts generally exhibit nonspecific symptoms. Persons at risk of infection include hunters, trappers, and those who handle ill wild animals. People working with sheep have been reported to be at high risk of pulmonary tularemia.[9]

Clinical practice implications

There are different clinical presentations of tularemia,[3] depending on the route of inoculation, the size of the inoculum, and the subspecies of *F. tularensis*. In BC, ulceroglandular disease accounted for 75% to 85% of all cases reported from 1940 to 1983.[2] The disease begins as a febrile illness

and is ultimately characterized by distal ulcerating lesions with regional lymphadenopathy that may resemble the bubo of bubonic plague.

Typhoidal tularemia (5% to 10% of cases) is a rare but severe form of the disease.[10] The acute illness is characterized by septicemia without cutaneous lesions or lymphadenopathy. It results from gastrointestinal infection following ingestion of the bacteria, with symptoms including nausea, vomiting, and bloody diarrhea.[10] The mortality rate of untreated cases is between 30% and 60%.[10]

The most serious form of the disease is pneumonic tularemia. This acute illness, which may result from inhalation of *F. tularensis* or as a complication of ulceroglandular or glandular disease, has a mortality rate approaching 60% when untreated. Since the clinical as well as the radiological presentations of pneumonic tularemia are highly variable, diagnosis can often be quite difficult.[10]

Gastrointestinal and oral-pharyngeal forms of the disease, acquired by ingestion of contaminated food or water, are characterized by cervical lymphadenopathy and a sore throat, sometimes with formation of a diphtheria-like pseudomembrane. Illness with this form of tularemia ranges from mild to severe if septicemia occurs.[10]

The incubation period of this infection is typically between 3 and 5 days, although it may be as short as 1 day and as long as 21 days.[3]

Treatment of this infection should be with aminoglycoside antibiotics, such as streptomycin or gentamicin, as the first-line agents.

Laboratory diagnosis

Multiple testing methods may be required in order to confirm the diagnosis of *F. tularensis*. The appropriate sample type for testing depends on the clinical presentation. The samples recommended for culture or direct molecular tests (or both) include blood, swabs from the primary lesions (ulcerative or necrotic skin), tissue from biopsy, lymph node aspirates, gastric washings, or respiratory samples from suspected patients prior to prescription of any antibiotics. Serology is another option to diagnose *F. tularensis*. A blood sample (7 to 10 mL) should be collected in a serum separator tube during the patient's first visit (acute stage) and a convalescent sample should be collected at least 2 weeks after the first sample. Other tests such as direct fluorescent assay can be done from the culture in order to confirm the diagnosis. Laboratory personnel should be consulted regarding an appropriate sample and notified when there is suspicion of *F. tularensis* because of the risk of laboratory-acquired infection.

Treatment

Treatment of this infection should be with aminoglycoside antibiotics, such as streptomycin or gentamicin, as the first-line agents. Combination of intravenous gentamicin and oral doxycylcine can successfully eradicate this pathogen. Tetracyclines and chloramphenicol can be used as well; however, tetracycline should not be used in children under 8 years of age or in pregnant or lactating women. Similarly, potential toxicity should be considered before using chloramphenicol. Other drugs, including quinolones, may also be effective. If the diagnosis, and therefore the treatment, is delayed, case mortality may be higher than the general North American estimate of 1%.[9]

Infection control and public health impact

Tularemia may be acquired by laboratory staff when exposed during organism culture.[7] It is important to communicate with the laboratory about potential cases so that appropriate precautions are taken. *F. tularensis* is considered a biosafety level 3 organism in Canada, with a known high potential for causing laboratory-acquired infections. Tularemia is not spread person-to-person, so no special infection-control precautions are required in hospitalized cases.

Public health has several roles to play in the prevention and follow-up of this infection. Communications that alert members of the public to the risks associated with being exposed to insects or handling wildlife can be carried out on a regular basis, particularly in rural areas known to be endemic.

Several of the cases in this review followed direct contact with wildlife, most often in the form of a bite from an infected animal. Infection can be prevented by educating people at high risk (animal handlers, trappers, and farmers who are exposed to infected animals and to insect vectors that harbor disease) and encouraging people to avoid exposure to insects in endemic areas.

Because *F. tularensis* is highly infectious, can be easily disseminated, and may cause serious disease, the organism is considered a possible weapon of bioterrorists and is included on a Centers for Disease Control and Prevention list of critical biological agents.[11] All cases, particularly those linked in time and space, should be followed up immediately with appropriate notification of public health officials.

Summary

Tularemia is a rare but potientially life-threatening infection caused by *F. tularensis*, a bacterium endemic in BC. Most commonly, tularemia presents with skin lesions and lymphadenopathy; severe bloodstream and pulmonary infections may also occur. All cases identified in this study were acquired in rural areas or involved patients residing in the Interior or Northern health authorities. Infection occurred most often from May to October.

Physicians, particularly those practising in rural areas, should be aware of this infection. In clinically and epidemiologically compatible cases, they should provide appropriate samples for cultures and for molecular and serologic testing in consultation with their local medical microbiologist or the provincial public health laboratory. Public health officials should also educate those at risk of coming into contact with this organism by handling infected wild animals or being exposed to insects. Patients with tularemia should be treated with aminoglycoside antibiotics.

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Competing interests

None declared.

Acknowledgments

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