CLINICAL CASE REPORT

Two cases of tularemia in hunters from rural Newfoundland

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BACKGROUND: Tularemia is a rare zoonosis caused by *Francisella tularensis,* a small gram-negative intracellular coccobacillus. Transmission occurs through direct contact with small mammals such as hares and rabbits, exposure to ticks, or ingestion or inhalation of aerosolized particles. It is a highly variable disease with six subtypes based on clinical features. Tularemia is a very rare disease in Canada, with only 0.01 cases per 100,000 people reported in 2017. **METHODS:** In this case report, we describe two cases of tularemia affecting hunters from rural Newfoundland and Labrador. **RESULTS:** The first case describes a patient with glandular tularemia diagnosed with serology; the second describes a patient with typhoidal tularemia diagnosed on blood culture. Both patients recovered after treatment with gentamicin. **DISCUSSION:** These cases highlight the importance of eliciting a careful social history from patients presenting with an unexplained febrile illness. Tularemia should be considered in the differential diagnosis of fever after hunting in rural areas.

KEYWORDS: Francisella tularensis, gentamicin, lymphadenitis, snowshoe hare, tularemia

HISTORIQUE : La tularémie est une zoonose rare causée par le *Francisella tularensis*, un petit coccobacille intracellulaire à Gram négatif. La transmission se produit par contact direct avec des petits mammifères comme des lièvres et des lapins, l'exposition aux tiques, l'ingestion ou l'inhalation de particules aérosolisées. C'est une maladie extrêmement variable possédant six sous-types en fonction des caractéristiques cliniques. La tularémie est une maladie très rare au Canada; seulement 0,01 cas sur 100 000 habitants a été signalé en 2017. **MÉTHODOLOGIE :** Dans le présent rapport de cas, les auteurs décrivent deux cas de tularémie chez des chasseurs de régions rurales de Terre-Neuve-et-Labrador. **RÉSULTATS :** Le premier cas décrit un patient atteint de tularémie glandulaire diagnostiquée par sérologie et le deuxième, un patient atteint d'une tularémie typhoïde diagnostiquée par culture sanguine. Les deux patients se sont rétablis après avoir été traités à la gentamicine. **DISCUSSION :** Ces cas font ressortir l'importance d'une histoire sociale attentive des patients qui ont consulté à cause d'une maladie fébrile inexpliquée. Il faut envisager une tularémie lors du diagnostic différentiel de fièvre chez des personnes qui ont chassé dans des régions rurales.

MOTS-CLÉS : Francisella tularensis, gentamicine, lièvre d'Amérique, lymphadénite, tularémie

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CASE PRESENTATION

Case 1

A 35-year-old man from rural Newfoundland and Labrador presented to the local emergency department with a 2-day history of fever, headache, sore throat, and a tender right axillary mass. He was previously healthy, with no relevant medical history and no regular medications. On initial assessment in the emergency department, he was given a clinical diagnosis of bacterial lymphadenitis and discharged on oral clindamycin. Blood and urine cultures were negative. He re-presented 2 days later with worsening of his symptoms, with new nausea and vomiting. Further history revealed he had been hunting

moose and snowshoe hares 1 week before his illness, which was of unclear significance at the time. He was prescribed oral amoxicillin–clavulanic acid and again discharged.

He returned for his third presentation the following day, having rigours with a temperature of 39.1°C, despite treatment with antipyretics. Heart rate was 120 beats per minute (bpm), blood pressure was 132/71 mmHg, and oxygen saturation was 98% on room air. On examination, he was in moderate distress. Neurologic examination was normal, with no meningismus. There was a tender, erythematous, and fluctuant right axillary mass measuring approximately 6 cm in diameter. There was a small abrasion on his right index finger, without proximal lymphangitis. The patient revealed that he had punctured his finger with a snowshoe hare bone while cleaning a carcass 1 week earlier.

Admission bloodwork showed normal renal function and electrolytes, normal complete blood count except for lymphopenia (0.5×10^9/L), and a C-reactive protein level of 79 mg/L. The patient was transferred to a regional referral centre and admitted for further investigation and management. Computed tomography of the head and cerebrospinal fluid testing were normal. Blood and urine cultures were again negative. The infectious diseases service was consulted and advised empiric treatment with gentamicin for possible tularemia. The patient rapidly improved after initiation of gentamicin. He was discharged 5 days later and stepped down to oral doxycycline for 3 weeks. His right axillary lymphadenopathy resolved over the following week. Initial *Francisella tularensis* serology was negative, but convalescent serology was positive (titre >1:128) 1 month later, confirming the diagnosis of tularemia.

Case 2

A 76-year-old retired businessman from St. John's, Newfoundland and Labrador, presented to the emergency department with confusion after a 5-day history of nausea, diarrhea, and subjective fevers. His medical history was significant for hypertension and gout, treated with trandolapril and allopurinol. Symptoms began the day he returned from a 3-week hunting trip in rural Newfoundland during which he had killed a moose, 80 snowshoe hares, and 20 grouse. He had skinned, cleaned, cooked, and eaten the hare and grouse meat during the trip while consuming a moderate amount of alcohol.

In the emergency department, the patient was afebrile and hemodynamically stable. Heart rate was 76 bpm, blood pressure was 142/59 mmHg, and oxygen saturation was 98% on room air. He was hypovolemic on physical examination without any concerning skin lesions or lymphadenopathy. Laboratory investigations revealed hyponatremia (sodium 123 mmol/L) and elevated transaminases (aspartate transaminase 348 U/L, alanine transaminase 178 U/L). A complete blood count showed leukocytes 6.9×10^9/L, hemoglobin 155 g/L, and platelets 81×10^9/L. The patient was admitted to the internal medicine unit with suspected alcoholic hepatitis and was treated with intravenous fluids.

Post-admission day 1, he became acutely unwell with a temperature of 39.8°C and an altered level of consciousness. Investigations revealed a C-reactive protein level of 242 mg/L, ferritin of 84,217 µg/L, lactate dehydrogenase of 1,090 U/L, and a bloodwork pattern consistent with disseminated intravascular coagulation (international normalised ratio 1.91, d-dimer 2,998 ng/mL, fibrinogen 1.62 g/L, platelets 72×10^9/L). Renal function and lactate were within normal limits. Given his exposure history, the infectious diseases service was consulted, and he was started on empiric treatment for tularemia with gentamicin. The patient rapidly improved over the course of 24 hours after initiation of antibiotics. He was discharged home after 6 days of intravenous antibiotic therapy without oral stepdown. Blood cultures grew gram-negative coccobacillus on day 13 of incubation. The isolate was handled in a biosafety cabinet and referred to the National Microbiology Laboratory, where it was identified as *F. tularensis*.

DISCUSSION

Microbiology and epidemiology

F. tularensis is a fastidious gram-negative, pleomorphic, non–spore-forming, slow-growing coccobacillus that causes tularemia (1). It is endemic in rural areas in the Northern Hemisphere and is classified into two types (2). Type A (subspecies *tularensis*), endemic to Canada and the United States, is one of the most virulent bacteria described. Severe infection and death can occur with inhalation of as few as 10 organisms (3). The high virulence, stability in aerosolized form, and ease of mass production made it an agent of potential bioterrorism in World War II (4). Biosafety level 3 precautions must be followed when working with pure culture. Type A tularemia results from direct human contact with small mammals such as rabbits, hares, and rodents, which act as reservoirs for the disease. It can also be transmitted by arthropod vectors, including ticks and deer flies (5).

Type B (subspecies *holarctica*) occurs throughout the Northern Hemisphere but is predominantly found in Europe. It is associated with bodies of water and semi-aquatic animals such as beavers and muskrats. It is considered to be mainly a waterborne disease, but it can also be transmitted through direct animal contact (6). It is much less virulent and is nonlethal in humans (7).

Tularemia is currently a reportable disease throughout North America and Europe, having been removed from the

Canadian notifiable diseases list in 1982 and then re-added in 2002. The most recent data from the Public Health Agency of Canada in 2017 document only four cases of tularemia nationally, with an incidence of 0.01 cases per 100,000 people (8). In their most recent 2018 reports, the United States and European Union both report incidence rates of 0.07 cases/100,000 people (9–10).

Given the paucity of cases in Canada, provincial distribution is unknown. However, tularemia appears to be uncommon in Atlantic Canada. A review by Wobeser et al identified only 3 cases in which human tularemia was linked to rodent or lagomorph exposure in Atlantic Canada, out of 69 total cases nationally from 1929 through 2009 (4). In Newfoundland and Labrador, a total of 3 cases of tularemia have been published, occurring in 1981, 1983, and 1989 (11–12).

The tick species *Haemaphysalis leporispalustris* has established a resident population on the island of Newfoundland and is a known vector of *F. tularensis* (13). A study performed in Newfoundland from 2002 to 2003 investigated the role of ticks as vectors for zoonotic diseases, including tularemia (14). A total of 2,349 *H. leporispalustris* specimens were collected, with 80% found on live trapped snowshoe hares. None of the ticks or snowshoe hares demonstrated antibody to *F. tularensis*. This may be due to inadequate sample size or absence of the pathogen during the time frame of the study.

Clinical subtypes

The clinical manifestations of tularemia are extremely variable, with six clinical subtypes based on route of infection: ulceroglandular (most common), glandular, oculoglandular, oropharyngeal, pneumonic, and typhoidal (15). The ulceroglandular subtype involves an ulcerative lesion with regional lymphadenopathy, whereas glandular tularemia has lymphadenopathy without ulceration. The route of infection in both cases involves direct inoculation of the skin. In case 1, the patient presented with painful axillary lymphadenopathy on the ipsilateral side of a rabbit bone puncture to the finger, representing lymphatic spread (glandular tularemia).

Oculoglandular tularemia is an uncommon subtype accounting for only 1% of cases. It is acquired by direct inoculation of the eye through contact with a contaminated finger, splashes, or exposure to high-pressure aerosols. It presents with unilateral conjunctivitis, eyelid swelling, and mucopurulent discharge (16). Oropharyngeal tularemia is acquired from contaminated food or water and presents with exudative and ulcerative stomatitis and pharyngitis (17). Pneumonic tularemia is acquired through inhalation of aerosolized *F. tularensis,* which can occur from lawn mowing, brush cutting, handling infected carcasses, or working with live culture (18). It usually presents with cough, dyspnea, and chest pain (19).

Typhoidal tularemia is a severe systemic form, accompanied by altered mental status without features of the other subtypes and no specific route of infection (2). The patient described in case 2 fit this profile.

Diagnosis

Tularemia is difficult to diagnose because of its low incidence and wide variety of presentations, with non-specific examination and laboratory findings. Diagnosis is delayed due to slow growth of the organism and delayed antibody response. Blood culture is generally negative after 5 days of incubation, before the organism grows. Therefore, a high index of suspicion based on history is required for correct diagnosis (Table 1).

Diagnosis can be made either through isolation of *F. tularensis* from a clinical specimen, by serology, or by polymerase chain reaction. Serologic diagnosis requires a four-fold increase in titre of *F. tularensis* antibody between acute and convalescent sera or a titre of 1:160 or greater (18). Antibodies against *F. tularensis* do not become positive until 10–20 days post-infection, making serology results too slow for acute management (15). Culture of lymph node aspirates, respiratory secretions, and tissue from skin lesions may also be positive (2). The microbiology laboratory should be alerted in advance when tularemia is suspected so that prolonged incubation and biosafety level 3 precautions are used.

In case 1, infectious disease consultation should have been considered earlier than the third emergency department visit, given progressive clinical worsening and a history of animal exposure. Needle aspiration of the fluctuant axillary mass may have yielded a culture-based diagnosis. Consideration was given to drainage upon presentation to the regional referral centre; however, it was deferred due to rapid improvement of the patient after initiation of gentamicin.

Table 1: When to suspect tularemia infection

Outdoor activities with exposure to wild animals, especially rodents and small mammals
Bite from an infected tick, deerfly, or other insects
Exposure to animals that may have been ill or died within 21 days of acquisition
Recent acquisition or exposure to small mammal pets, including rodents, hares, or rabbits
Consuming undercooked wild game
Drinking well water in areas of no chlorination and possible contamination with dead rodents
Laboratory employee involved in handling tularemia specimens

Treatment

Treatment of tularemia depends on the severity of disease. For severe illness requiring admission to hospital, aminoglycosides (gentamicin or streptomycin) are the first-line treatment. Gentamicin 5 mg/kg intravenously or intramuscularly in two to three divided doses for a duration of 7–10 days is the most common regimen (20). For mild or moderate illness, often caused by Type B tularemia, oral treatment with doxycycline at a dose of 100 mg orally twice a day for 14–21 days is recommended. Ciprofloxacin 500–750 mg orally twice daily for 10–14 days has also been shown to be highly effective (21). In both cases 1 and 2, the patients rapidly improved on gentamicin. Tularemic meningitis represents hematogenous seeding of the central nervous system (CNS) and requires special treatment considerations. Although no clear guidelines exist, treatment with chloramphenicol plus streptomycin for 7–21 days has been shown to be the most effective regimen in reported cases (22). Combination therapy is recommended given poor penetration of aminoglycosides into the CNS.

CONCLUSION

Tularemia has a highly variable presentation and may be missed with routine testing. A thorough social history, including occupational, recreational, travel, and exposure history, is essential. A history of exposure to small mammals or ticks should prompt the consideration of tularemia. An infectious diseases specialist should be consulted when tularemia is suspected, and empiric treatment should be initiated. Routine empiric antibiotic regimens may not adequately cover *F. tularensis;* thus, patients often clinically worsen before appropriate antibiotics are initiated. The cases presented suggest that snowshoe hares could be a natural reservoir for tularemia in Newfoundland and that hunters are at risk for infection.

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