

Pharyngeal tularemia acquired in an urban setting in Canada

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In early June, a 49-year-old woman with a medical history of chronic obstructive pulmonary disease, anxiety and depression presented to an emergency department in Manitoba, Canada, with a 1-day history of sore throat, subjective fevers, chills and fatigue. On examination, the patient had obvious exudate over the right tonsil and swollen anterior cervical lymph nodes, which was consistent with a diagnosis of pharyngitis. A throat swab for bacterial culture was not obtained, and she was prescribed amoxicillin–clavulanate to treat for presumed group A *Streptococcus*.

Two weeks later, the patient returned to the emergency department with an increase in swelling to the right side of her neck. She had enlarged, tender lymph nodes in the right upper internal jugular deep cervical chain. A computed tomography (CT) scan of the neck showed right-sided necrotic lymphadenopathy. The otolaryngology performed fine needle aspiration of a lymph node for pathology and mycobacterial culture. The patient received another prescription for amoxicillin–clavulanate and was discharged with a plan to follow up with otolaryngology as an outpatient.

In early July, the patient presented for a third time with increased swelling to the right side of her neck, and the infectious diseases service was consulted. Her sore throat, fever and chills had all improved, and she did not have dyspnea, odynophagia or discomfort in her teeth. A review of systems was otherwise negative. She was afebrile and hemodynamically stable. On examination, she had only tender right cervical adenopathy, with an otherwise normal systemic examination. On further history, the patient indicated that she lived in Winnipeg, Manitoba, with her daughter and 3 grandchildren. She smoked cigarettes and reported consuming 1–2 alcoholic beverages a month. She had no history of recreational drug use. She was originally from Ontario but had not left Manitoba for many years and had not recently travelled. She gave no history of exposure to tuberculosis or tick bites.

The patient had 3 outdoor cats and 1 dog at her place of residence. About 2 weeks before her initial presentation, one of the cats was diagnosed with a skin infection, which subsequently improved with antibiotics. The patient did not recall any recent animal bites or scratches, however, and she had no contact with wild animals nor had she consumed any meat or organs of wild animals.

On laboratory testing, the patient had an elevated white blood cell count of 13.4 (normal 4.5 – 11) $\times 10^9/L$ and a C-reactive protein level of 28 (normal < 5) mg/L . A repeat CT scan of the patient's neck showed a substantial increase in the size of the right-sided

Key points

- Tularemia is an uncommon zoonotic disease caused by the fastidious gram-negative coccobacillus *Francisella tularensis*.
- Infections with *F. tularensis* are usually acquired in a rural setting from a tick or deerfly bite, contact with an infected animal (e.g., while skinning the animal) or via ingestion of contaminated food or water.
- The 6 classic clinical presentations of tularemia are ulceroglandular, glandular, oculoglandular, pharyngeal, typhoidal and pneumonic.
- A laboratory diagnosis of tularemia may be made by recovery of *F. tularensis* on culture, through serology or with a molecular assay.

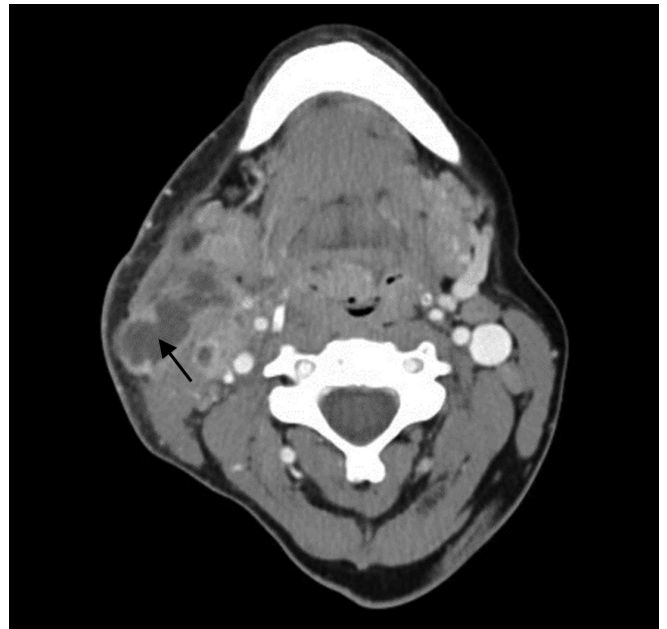


Figure 1: Computed tomography scan showing necrotic lymph nodes (arrow) in the right side of the neck of a 49-year-old woman with tularemia.

necrotic cervical lymph nodes (Figure 1). The patient was admitted to hospital by the otolaryngology service and underwent a bedside incision and drainage procedure, during which pus was aspirated. We thought the most likely diagnosis was either bacterial lymphadenitis with failure to respond to medical treatment

owing to a need for abscess drainage or cat-scratch disease. However, the differential diagnosis of cervical lymphadenopathy is broad and includes infectious (e.g., Epstein–Barr virus (EBV), cytomegalovirus (CMV), HIV, syphilis, tularemia and mycobacteria) and noninfectious (e.g., malignant disease) causes.

We submitted a sample of purulent material from the patient's necrotic lymph node for bacterial, fungal and mycobacterial culture, as well as cytology. We obtained sputum for mycobacterial culture and sent serum samples for serologic tests for EBV, CMV, HIV, syphilis, and *Bartonella* and *Francisella* species. Pending the results of these investigations, we started empirical treatment with ceftriaxone and metronidazole for coverage of common bacteria, including oral anaerobes, and azithromycin, for empiric coverage of *Bartonella henselae*.

Because of a slow clinical response, the patient underwent an operative incision and drainage procedure and a right tonsillectomy 6 days after she was admitted. She was clinically well after the procedure and we discharged her with a course of amoxicillin–clavulanate. Culture of the fluid obtained on admission yielded only coagulase-negative staphylococci, which was presumed to be a contaminant. However, shortly after discharge, the patient's serologic test result returned positive for *Francisella tularensis* (titre 1:5120). All other serological investigations were negative. A sample of purulent fluid that remained in the clinical microbiology laboratory was forwarded on to a reference laboratory (National Microbiology Laboratory, Winnipeg) for molecular detection of *F. tularensis*.

The reference laboratory identified *F. tularensis* subsp. *holarctica* using a real-time polymerase chain reaction assay. We thought our patient most likely had pharyngeal tularemia, given the history of an exudative pharyngitis at symptom onset. We stopped treatment with amoxicillin–clavulanate and prescribed a 14-day course of ciprofloxacin. Two weeks later, the swelling and tenderness had improved, and the purulent discharge had stopped.

Discussion

Tularemia is a zoonosis caused by *F. tularensis*, a slow-growing, fastidious, aerobic, gram-negative coccobacillus.^{1–4} Infections caused by *F. tularensis* remain uncommon in Canada. Tularemia was added to the Canadian list of notifiable diseases in 1930; it was removed in 1982 and then added back to the list in 2002.⁵ Between 2003 and 2019, only 157 reported cases of tularemia were reported in Canada, with the number of cases ranging between 5 and 22 per year (about 9 cases reported annually on average).⁵ Human tularemia cases have been reported in all Canadian provinces.

Francisella tularensis is able to infect many different vertebrates and arthropods.³ Wild animals, rodents and lagomorphs (e.g., rabbits and hares) are thought to be the key reservoirs and amplification hosts.^{1,2} Arthropods have been implicated in the mechanical transmission of this organism.^{1–3,6} Humans can become infected after a tick or deerfly bite, contact with an infected animal (e.g., when skinning the animal), ingestion of an undercooked infected animal, or via ingestion of contaminated water or food.^{1,3,6} Aerosolization of *F. tularensis* with subsequent inhalational exposure has been described related to landscaping activities.¹ Occupations that may pose a risk for infection with *F. tularensis* are listed in Table 1.³ Infections are more frequent among men, which may be related to participation in at-risk activities.^{1,3}

Most infections with *F. tularensis* are acquired in a rural setting.¹ Urban cases, such as in our patient, are uncommon. However, *F. tularensis* has been recovered from animals within urban parks in Saskatoon, Saskatchewan (which borders Manitoba), therefore, it is plausible that infected animals may also be found within the city limits of Winnipeg.⁸ It remains unclear how our patient became infected with this pathogen, as there was no history of arthropod exposure, and the patient reported no participation in activities known to be associated with a risk of this infection. However, the

Table 1: Overview of tularemia^{1–4,7}

Consideration	Key point
Pathogen	<i>Francisella tularensis</i> subspecies <i>tularensis</i> and subspecies <i>holarctica</i>
Relevant exposures	Tick or deerfly bite, contact with an infected animal, ingestion of contaminated food or water, occupational exposure (e.g., farmers, hunters, veterinarians, landscapers, meat handlers and laboratory workers), travel or area of residence (typically occurs as a rural disease)
Incubation period	Average of 3–5 d, range of 1–21 d
Seasonality	Most commonly acquired during the summer months
Classic clinical syndromes	Ulceroglandular (most common), glandular, oculoglandular, pharyngeal, typhoidal, pneumonic
Diagnostic criteria	Confirmed case <ul style="list-style-type: none"> • Compatible clinical presentation and either recovery of <i>F. tularensis</i> on culture from an appropriate clinical specimen or a fourfold or greater change in <i>F. tularensis</i> serum antibody titres Probable case <ul style="list-style-type: none"> • Compatible clinical presentation and one of the following: detection of <i>F. tularensis</i> in a clinical specimen by a fluorescent assay, a single serum sample (serology) with a microagglutination titre of $\geq 1:128$ or a tube agglutination titre of $\geq 1:160$, or detection of <i>F. tularensis</i> nucleic acid with a molecular assay
Treatment	Severe disease <ul style="list-style-type: none"> • Gentamicin or streptomycin Mild-to-moderate disease <ul style="list-style-type: none"> • Ciprofloxacin or doxycycline

patient did live with outdoor cats and a dog, and domestic cats have been implicated infrequently in the acquisition of tularemia.^{3,9} *Francisella tularensis* may be carried in the mouth of a cat or on its claws after it has killed or fed on infected prey, which could lead to mechanical transmission.³ Reports exist of contact with dogs that resulted in tularemia through either mechanical transmission (e.g., biting, snuggling or licking), contact with dead animals retrieved by a dog or contact from infected ticks acquired from a dog.⁹ It is possible that one of the patient's pets inadvertently contaminated water or food that she subsequently ingested. One of the cats had a recent cutaneous infection. It is also possible that this was caused by *F. tularensis* and the patient then became infected from contact with the lesion.

The typical incubation period and 6 classic forms of tularemia are listed in Table 1.^{1,3,4} Pharyngeal tularemia is caused by oral acquisition of *F. tularensis*.^{3,4} Patients with pharyngeal tularemia present with fever and pain in the throat. On examination, an exudative pharyngitis, often with 1 or more ulcers, and cervical lymphadenopathy is seen.³ If treatment is delayed, cervical adenopathy may become the dominant manifestation, without an associated pharyngitis.³ We speculate that this is what occurred with this patient, as an exudative pharyngitis was documented on initial presentation but was no longer observed 5 weeks later when she was admitted to hospital.

Tularemia can be difficult to diagnose, as in this case. In 1 case series, 68% of patients with ulceroglandular, glandular or pharyngeal tularemia were initially diagnosed with another more common infection.¹⁰ Laboratory confirmation of tularemia can be achieved by recovery of *F. tularensis* on culture, through serology or molecular methods (Table 1).^{1,7} In Canada, serological and molecular detection of *F. tularensis* are both offered at the National Microbiology Laboratory. It is important to recognize that this organism is a risk group 3 pathogen, and laboratory-acquired infections may occur if proper containment protocols are not followed.^{1,3} Therefore, clinicians should alert the microbiology laboratory if tularemia is being considered in the differential diagnosis for a given patient.

Francisella tularensis isolates are generally susceptible in vitro to aminoglycosides, fluoroquinolones and tetracyclines.¹¹ Streptomycin or gentamicin for a duration of 7–10 days are typically recommended for the treatment of severe disease.³ Mild-to-moderate infections may be treated with either ciprofloxacin for 10–14 days or doxycycline for 14–21 days.³ Some observational studies have suggested higher cure rates with ciprofloxacin relative to doxycycline.^{10,12} We chose ciprofloxacin as treatment for this patient based on data from these reports. In retrospect, our patient's non-improvement on amoxicillin–clavulanate was a clue that her infection may have been caused by a less common pathogen.

Conclusion

We present a case of probable pharyngeal tularemia acquired in an urban setting in Canada. When tularemia is considered in the differential diagnosis, key questions to ask on history include place of residence, recent travel, animal contact, occupation, hobbies and history of recent tick or fly bites. This case was unusual in that the patient did not report any exposures that are generally associated with infection caused by *F. tularensis*, despite having a clinical syndrome that was quite consistent with tularemia. Physicians should

be aware of the clinical manifestations of this uncommon but serious infection so that appropriate diagnostic testing is pursued in patients presenting with compatible symptoms, especially when more typical pathogens have been excluded.

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