Glandular tularemia in a Native American child

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Abstract
This case report details the clinical manifestation and course of glandular tularemia, an uncommon but significant cause of cervical lymphadenopathy in children. We discuss the unique attributes of this disease along with appropriate steps that lead to early identification of the organism and effective treatment. The potential use of the organism as a bioterrorism agent is another interesting aspect of this entity.

Introduction
Children with infectious cervical lymphadenopathy are frequently seen by pediatricians and family practitioners. The etiologic agents in most cases are commonplace, and the diagnosis and treatment are straightforward. But some rare cases require a more thorough approach to identification of the pathogen and the attention of a surgical specialist for biopsy or incision and drainage of an abscess.

One uncommon but significant cause of cervical lymphadenopathy in children is glandular tularemia. The causative pathogen—Francisella tularensis—is of interest for several reasons. First, making a definitive microbiologic identification of F. tularensis is challenging because of its fastidious growth characteristics and potential hazard to laboratory workers. Moreover, the risk of morbidity and mortality in patients with glandular tularemia is best minimized by specific antimicrobial therapy that is not usually considered for the more common causes of infectious lymphadenopathy. Finally, F. tularensis is considered a potential bioterrorism agent because of its virulence, transmissibility as an aerosolized agent, hardiness in nature, and ability to cause illness with only a small amount of inoculum.

In this article, we describe a case of glandular tularemia in a child, and we review the physical, laboratory, and radiologic findings of this disease as well as the response to medical and surgical therapy.

Case report
A 3-year-old Native American boy was brought to a family physician with symptoms of an upper respiratory tract infection and increasing fever. His medical history was unremarkable, and his immunizations were up to date. He was initially treated with amoxicillin, acetaminophen, and ibuprofen. However, 2 days later, his fever had risen to 105.2°F, and he had developed a 3 × 4-cm left upper cervical swelling that featured a red streak. Laboratory studies revealed that his white blood cell (WBC) count was 4,640/mm³, his segmented neutrophil level was 43%, his band neutrophil level was 18%, his lymphocyte level was 31%, and his monocyte level was 8%.

The boy was admitted to a community hospital and started on intravenous cefotaxime at 500 mg every 8 hours, but he remained febrile and irritable. He was transferred to the Department of Pediatrics at Avera Sacred Heart Hospital in Yankton, S. Dak. Examination there revealed that the 3 × 4-cm tender mass was located deep to the superior sternocleidomastoid muscle and that the patient’s left tympanic membrane was erythematous. His temperature was 102°F, his WBC count was 4,700/mm³, his band neutrophil level was 17%, and his C-reactive protein level was 10.8 mg/dl (normal: 0.5 to 1.0); a screening test for streptococcal infection was negative. Chest x-ray detected some cardiac enlargement and distention of the pulmonary vessels. Computed tomography (CT), with and without contrast, identified the 3-cm rim-enhancing mass deep to the sternocleidomastoid (figure 1).

An otolaryngologist was consulted, and the next day the patient was taken to the operating room. During surgery, a multinodular, thick-walled, abscessed lymph node was drained, and necrotic tissue was removed for histologic examination. Stained cultures were obtained to look for aerobic and anaerobic organisms and tuberculosis. Postoperatively, the patient was administered IV clindamycin at 150 mg every 6 hours and IV cefotaxime at 500 mg every 8 hours.

Initially, the patient showed slight improvement. However, by the time his Penrose drain was removed 48 hours after surgery, his mass persisted, his temperature was 102°F, his WBC count was 21,000/mm³, and runs of
bradycardia (48 to 50/min) were noted. In the initial culture and sensitivity report, the pathologist suggested a *Hemophilus* species as a possible pathogen, and the histologic analysis found widespread necrotizing acute inflammation (figure 2).

The pathologist entertained the possibility of cat-scratch disease, and recommended that additional tests be performed to search for a bacteriologic source. One week after surgery, a reference laboratory in Salt Lake City identified *F. tularensis* in the abscess fluid, which established the diagnosis of glandular tularemia. The patient was treated with IV gentamicin at 60 mg every 12 hours for 2 weeks, and his symptoms resolved completely. During the patient's recovery, his mother noted that the boy often played with several feral cats that frequented the area around their home. These cats were most likely the vector for the infection.

**Discussion**

Glandular tularemia is one of six clinical syndromes in humans that manifest as infection by *F. tularensis* (table); these six are distinguished by their mode of transmission and portal of pathogen entry. The first report of *F. tularensis* infection was reported in 1911 by McCoy, who found it in rodents that had contracted a plague-like disease in Tulare County, Calif.1 McCoy called the organism *Bacterium tularensis*. In 1921, Francis noted seven bacteriologically confirmed cases of naturally occurring tularemia and other cases of laboratory-acquired illness.1 Parker and Spencer discovered the role of ticks in the transmission of tularemia in 1924.1 Ohara described the disease in Japan in 1925, and he was able to reproduce it by voluntary inoculation of his wife.2 In recognition of Francis's lifelong contributions to the study of tularemia, the American Medical Association nominated him for the Nobel Prize in Medicine. In 1959, the name of the organism's genus was changed to Francisella.

**Epidemiology.** Tularemia is almost exclusively a rural disease, and it has been reported in 49 states nationwide (no case has been reported in Hawaii). Between 1990 and 2000, 1,368 cases in 44 states were reported to the Centers for Disease Control and Prevention (CDC); four states accounted for 56% of all cases: Arkansas (23%), Missouri (19%), South Dakota (7%), and Oklahoma (7%). The incidence of tularemia has declined markedly from thousands of cases per year during the first half of the 20th century to hundreds of cases annually since 1950.3,4

A variety of small mammals—rabbits, mice, moles, and squirrels in particular—serve as natural reservoirs of *F. tularensis*, which they acquire through bites by ticks, flies, and mosquitoes or by contact with contaminated soil or water. Transmission to humans can occur by several means: direct contact with infected tissue (e.g., while cleaning rabbits), insect bites, inhalation of hay or straw dust, and ingestion of contaminated meat or water.3 There appears to be a bimodal seasonal trend, as arthropod-borne transmission is more common in the spring and summer and transmission during hunting activities is more common in the winter.

Laboratory workers are especially vulnerable to *F. tularensis* infection, either by inhaling aerosolized organisms in culture media or by accidental inoculation. Person-to-person spread has not been documented. Organisms can remain viable in the environment for many weeks, but they are sensitive to heat and unable to survive in boiled water or meat cooked at 133° F for 10 minutes.

**Microbiology.** *F. tularensis* is a small (0.2 to 0.7 mm), aerobic, gram-negative coccobicillus that exists in vivo as a facultative intracellular pathogen. Its two major subspecies (biovariants) are *F. tularensis* biovar tularensis (type A), the more virulent form that is most common in North America, and *F. tularensis* biovar palaearctica (type B), a relatively avirulent form that is found in Europe and Asia.6 *F. tularensis* type A causes 90% of all reported
Table. The six forms of tularemia and their relative incidence

<table>
<thead>
<tr>
<th>Clinical syndrome</th>
<th>Relative incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulceroglandular tularemia</td>
<td>80%</td>
</tr>
<tr>
<td>Glandular tularemia</td>
<td>15%</td>
</tr>
<tr>
<td>Oropharyngeal tularemia</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Oculoglandular tularemia</td>
<td>1%</td>
</tr>
<tr>
<td>Typhoidal tularemia</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Pneumonic tularemia</td>
<td>&lt;1%</td>
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</tbody>
</table>

cases of tularemia in the United States. This fastidious organism grows slowly, and its identification requires special nutritionally supported media. The 1-mm opaque colonies usually appear after 24 to 48 hours of incubation at 37°C in cysteine-enriched broth, thioglycollate broth, cysteine heart-blood agar, buffered charcoal-yeast agar, or chocolate agar. Because growth can be delayed, cultures should be held at least 10 days. Clinicians who suspect tularemia should alert laboratory personnel of their suspicion so that they can implement the appropriate culture techniques and take steps to minimize the risk of acquiring this hazardous pathogen themselves. Once growth of the organism is determined, the culture should be transferred to a biosafety level III laboratory environment—that is, one that features double door entry, inward airflow, and air that is not recirculated.

Pathogenesis and clinical appearance. In a consensus statement on tularemia, Dennis et al called F. tularensis “one of the most infectious pathogenic bacteria known, requiring inoculation or inhalation of as few as 10 organisms to cause disease.” Invasion takes place through the skin, mucosa, gastrointestinal tract, or lungs. After invasion, the intracellular organisms multiply and spread to regional lymph nodes, then disseminate to other organs. The initial tissue reaction involves an intensely supplicative necrosis and accumulation of polymorphonuclear leukocytes, followed by invasion of macrophages, epithelioid cells, and lymphocytes as the suppurative lesions become granulomatous. Cell-mediated immunity plays an important role in combating this and other intracellular pathogens, such as Legionella, Listeria, Brucella, and Mycobacterium species, which can be eliminated only after the ingesting macrophages are activated by T lymphocytes. Humoral immunity does not seem to play a significant protective role. The clinical manifestation varies from asymptomatic illness to fulminant toxemia with septic shock. After an incubation period of 2 to 14 days, symptoms begin with an abrupt onset of fever (100°F to 104°F), headache, chills, rigor, body aches, coryza, and sore throat. As was the case with our patient, the glandular form of tularemia involves adenopathy, usually cervical in the deep jugular chain without an apparent skin lesion. Some 42% of such cases feature bradycardia associated with high fever (pulsetemperature dissociation)—again as occurred in our patient.

The typhoidal form of tularemia involves severe systemic illness in the absence of signs that would indicate the site of inoculation or the anatomic localization of the infection. The pneumonic form can be caused by inhalation or by hematogenous spread of the pathogen from other sites. A finding of either typhoidal or pneumonic tularemia, especially in an urban setting, would raise the specter of an act of bioterrorism. Mortality rates of 30 to 60% have been reported in patients with untreated systemic tularemia, although the current case fatality rate in the United States is less than 2%. Diagnosis. Considering the difficulty of identifying F. tularensis by routine microbiologic screening protocols, it is incumbent upon the practitioner to suspect the disease when clinical findings are suggestive. The next steps are to collect appropriate specimens and alert the laboratory to the need for special diagnostic and safety procedures. In addition to the clinical picture that characterizes tularemia, characteristic radiographic signs of tularemia cervical lymphadenopathy may be seen on contrast-enhanced axial CT. Low-density, rim-enhancing lesions typically involve the upper jugular chain, as was the case with our patient, and standering of subcutaneous fat is not seen, unlike the case with the more common acute pyogenic abscess. In tissue specimens, small pleomorphic light-staining rods can be identified by light microscopy and are easily distinguishable from bipolar-staining Yersinia pestis and the large gram-negative rods of Bacillus anthracis.

Microscopic demonstration of F. tularensis using fluorescence-labeled antibodies is a rapid diagnostic procedure that is performed in designated reference laboratories. The most productive culture media for identifying F. tularensis were noted earlier in this article, but several studies have concluded that newer techniques—such as polymerase chain reaction, enzyme-linked immunoassays, and pulsed-field gel electrophoresis (in reference laboratories)—may be quicker and more sensitive. Serum antibody levels are useful for epidemiologic purposes, but not for managing an outbreak because the diagnostic finding of a four-fold increase in antibody titters is not evident until 2 weeks after the onset of symptoms. Treatment. Treatment protocols appear to be based on case reports and anecdotal experience. The best option in terms of efficacy and availability is IV gentamicin at 5 mg/kg twice daily for 10 days. Suspected cases should be treated empirically pending laboratory confirmation. IV doxycycline at 100 mg twice daily for 14 days is a second-line option, and IV ciprofloxacin at 400 mg twice daily for 10 days has been described as effective in multiple reports. Oral ciprofloxacin at 15 mg/kg/day in two divided doses has also been shown to be satisfactory in
Vaccination provides only incomplete protection and is recommended only for laboratory personnel who routinely work with this organism. Isolation of infected patients is not necessary. In conclusion, our case was marked by several distinguishing characteristics, knowledge of which may alert the clinician to consider a diagnosis of glandular tularemia rather than one of the more common pyogenic cervical adenopathies. These features included the patient's environment, physical findings such as pulse-temperature dissociation, the characteristic radiographic finding on CT, the initial histology, and the lack of response to initial treatment. Based on our experience and reports from South Dakota and other states, fever, cervical lymphadenopathy, and malaise appear to be important clinical features of tularemia in children. Another aspect of this disease worth noting is that typhoidal or pneumonic tularemia, especially in non-endemic areas, should suggest the possibility of an act of bioterrorism. Information regarding testing, handling, and shipping of specimens can be obtained from personnel at the CDC's Division of Vector-Borne Infectious Diseases in Fort Collins, Colo. They can be reached by phone ([970] 221-6400) or e-mail (dvbid@cdc.gov).

References

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