Tularemic Meningitis in the United States

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**Background:** Tularemia is a zoonotic disease caused by *Francisella tularensis*. Tularemia presents with various clinical illnesses, but meningitis is rare.

**Objectives:** To describe a patient who developed typhoidal tularemia with atypical acute meningitis and to review the pathogenesis, clinical and laboratory features, and antibiotic drug treatment of reported cases of tularemic meningitis.

**Design:** Case study and literature review.

**Setting:** University hospital, tertiary care center.

**Patient:** A 21-year-old healthy man who had recently worked as a professional landscaper in the Albuquerque, New Mexico, metropolitan area developed fever, malaise, headache, and a stiff neck.

**Main Outcome Measures:** *Francisella tularensis* cerebrospinal fluid culture, antibiotic sensitivity, transmission source, and outcome.

**Results:** The cerebrospinal fluid contained a lymphocytic pleocytosis, negative Gram stain, and *F tularensis* isolation with chloramphenicol and streptomycin antibiotic sensitivities.

**Conclusions:** Although tularemia is uncommon and tularemic meningitis is rare in the United States, attention is drawn to the increasing number of cases in professional landscapers, the atypical cerebrospinal fluid picture, and unusual antibiotic sensitivities.

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**REPORT OF A CASE**

A 21-year-old previously healthy man presented to the emergency department in October 2006 with 7 days of a cough productive of black and yellow sputum, subjective fevers, chills, myalgias, and chest tightness with pleuritic chest pain. For 3 days before admission, he had a progressively worsening headache with neck stiffness and 1 day of 8 episodes of watery diarrhea. The patient reported that he had taken amoxicillin orally for 1 day. He had recently changed jobs and did not initially report that he had worked as a professional landscaper until 7 days before the onset of symptoms. He had performed lawn mowing and leaf blowing services and noted that he had seen dead rabbits in the areas in which he worked.

His temperature was 39.6°C. He was alert and oriented to time, place, and person. He had a stiff neck, without weakness or sensory loss. Bibasilar crackles with expiratory wheezing were noted. There were no lymphadenopathy, skin lesions, or ulcerations. Cranial computed tomography...
phy findings were normal. Abnormal laboratory test results included a white blood cell count of 10 400×10⁹/L (to convert to ×10⁹ per liter, multiply by 0.001) (78% neutrophils) and an erythrocyte sedimentation rate of 40 mm/h. The cerebrospinal fluid (CSF) had a total nucleated cell count of 1416/mm³, with 19% neutrophils and 73% lymphocytes, and a red blood cell count of 23×10⁸/µL (these conversions are for blood; don’t apply to CSF). The CSF glucose concentration was 41 mg/dL, and the total protein level was 2660 g/dL. The concurrent serum glucose level was 123 mg/dL. Gram staining of CSF sediment was negative. Findings from chest radiography were normal. Magnetic resonance imaging showed cerebellar tonsillar herniation consistent with Chiari type 1 malformation without evidence of brainstem syrinx.

The patient was initially treated with intravenous ceftriaxone sodium and vancomycin hydrochloride. On hospital day 4, the patient’s headache became worse, and he reported diplopia and nausea. A repeated lumbar puncture demonstrated an opening pressure of 490 mm of CSF and a total nucleated cell count of 2590/mm³, with 32% neutrophils, 43% lymphocytes, and 25% monocytes. The glucose level was 28 mg/dL, the total protein level was 2950 g/dL, and the Gram stain was negative. The concurrent serum glucose level was 128 mg/dL (to convert to millimoles per liter, multiply by 0.0555).

On hospital day 4, the initial CSF culture grew a gram-negative cocccobacillus that was confirmed to be Francisella tularensis by the New Mexico State health laboratory the following day, and subtype analysis was not performed. Use of the other antibiotic agents was stopped, and the patient was treated with intravenous chloramphenicol sodium succinate, 1 g every 12 hours, and intravenous streptomycin sulfate, 1 g every 12 hours, for 14 days, followed by 14 days of oral ciprofloxacin hydrochloride, 750 mg twice daily. The patient showed clinical improvement within 48 hours, and he eventually had complete resolution of symptoms. On 8-month follow-up, the patient’s only complaint was fatigue, his physical examination findings were normal, and his Francisella tularensis serum antibody titer was 1:1024 by means of microagglutination testing.

**COMMENT**

Tularemnic meningitis is rare; only 16 cases have been reported (Table). The worldwide incidence of tularemia is unknown and likely underrecognized. Tularemia not infrequently occurs in the United States and other developed countries in the northern hemisphere. Between 1990 and 2005, 2000 human cases from 44 states were reported to the Centers for Disease Control and Prevention. ¹²,¹⁷

The early clinical picture of tularemnic meningitis may be relatively nonspecific. Most cases occur in late spring and summer,²¹ when individuals are exposed to infected arthropods (ticks and biting flies) or to aerosolized bacteria from handling hay, cutting brush, or mowing over dead infected animals. ²²,²³ Occupational exposure has been reported in landascapers in Martha’s Vineyard in Massachusetts, with an outbreak of 59 cases of mostly pulmonary tularemia beginning in 2000 and continuing through 2006.²⁵ A serosurvey of landscapers in Martha’s Vineyard reported F. tularensis antibody titers in up to 15% of workers, and the highest titers were in those who mowed grass, cut brush, and used a power blower.²⁴ Winter outbreaks also occur, although more rarely, and are usually related to hunters coming in contact with infected animal carcasses.²¹ Cases of tularemia have been reported from 44 states, but 56% of all cases are reported from Arkansas, Missouri, South Dakota, and Oklahoma.²¹

_Francisella tularensis_ is highly infectious, requiring as few as 10 inhaled bacteria to cause disease, making aerosolization an environmental risk and a potential mode of transmission as a bioterrorist agent.²⁶ Francisella tularensis was studied in several countries as a potential bioterrorist agent and was weaponized by the US military in the 1950s to 1960s as part of an offensive biowarfare program.²⁷ The US military terminated its biological weapons development in 1970, and all stockpiles were destroyed by 1973.²⁷ Francisella tularensis is classified as a class A bioterrorist agent due to its potential ease of dissemination and high morbidity and mortality. All human cases of tularemia must be reported to the Centers for Disease Control and Prevention.²⁸ Postexposure prophylaxis with ciprofloxacin, 500 mg orally twice daily, or doxycycline hyclate, 100 mg orally twice daily, for 14 days is thought to be protective against symptomatic infection.²⁷

The incubation period of tularemia is usually 3 to 6 days, but it may range from 1 to 14 days after inoculation.²⁷ In patients with tularemnic meningitis, signs and symptoms of meningitis typically developed 5 days after the onset of initial illness but ranged from 3 to 30 days. Seven patients with meningitis presented with ulceroglandular disease, defined as ulcers on the skin with regional lymph node enlargement. Five patients had the typhoidal form, characterized by an influenza-like syndrome with chills, fever, headache, and generalized aches without lymphadenopathy, skin ulcers, or pneumonia. Four patients had pharyngeal disease (painful sore throat with enlarged tonsils and formation of a yellow-white pseudomembrane). In this series with often incomplete histories and examinations, most patients had confusion, headaches, meningismus, and fevers. Seizures were reported in only 1 patient. Our patient had some symptoms consistent with typhoidal tularemia, but he also had symptoms consistent with possible pneumonia, with crackles and wheezing on physical examination but negative findings on chest radiography. The patient most likely acquired his infection through inhalation as a landscaper.

In tularemnic meningitis, patients usually had marked CSF pleocytosis, with a mean white blood cell count of 1788×10⁹/L (range, 2-13 200×10⁹/L). In contrast to most other causes of acute bacterial meningitis, in tularemnic meningitis, there was usually a mononuclear predominance ranging from 70% to 100%. Levels of CSF glucose were depressed, with a mean of 32 mg/dL (range, 9-59 mg/dL). The mean CSF protein level was 3600 g/dL (range, 230-18 900 g/dL). In addition, as was found in our patient, the Gram stain of CSF sediment was negative in 90%. Although the reason for the low sensitivity
of Gram staining is unclear, it may reflect that an F
tularensis Gram stain is weak, is intracellular, or is in low
numbers in the CSF (<10^3 colony-forming units/mL).20,21
Patients with tularemic meningitis had similar blood
changes as patients with tularema without meningitis.
Some peripheral white blood cell counts were normal,
but most were elevated (range, 3000-49,000/µL),
with a mononuclear predominance.

The differential diagnosis of mononuclear pleocytosis
is broad. Viral infections, including herpes simplex
virus, may cause a mononuclear predominance; how-
ever, it would be expected that the CSF would have an
elevated glucose level. Other etiologies include Myco-
bacterium and Cryptococcus; however, these infections
would be expected in immunocompromised hosts. Spi-
rochete infections with Treponema pallidum or Borrelia
burgdorferi may also cause mononuclear pleocytosis along
with other infections, including Brucella, Bartonella
henselae, and Leptospira. Our patient did not have risk
factors for these diseases.

Isolation of F tularensis is difficult and slow because
F tularensis is fastidious. Most isolates appear in 2 to 4
days, but it may take as long as 14 days to grow in cul-
ture.22,23 In our patient, CSF isolation required 4 days,
and the blood specimen did not grow the organism. It is
important to notify the microbiology laboratory of sus-
pected tularemia so that they will take appropriate safety
precautions and hold the cultures longer. Routine clini-
ical specimens require a biosafety level 2 laboratory, but
further processing of initial isolates suspected of being

Table. Case Histories of Tularemia Meningitis

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient Sex/Age</th>
<th>Work</th>
<th>Presumed Source of Infection</th>
<th>Days From First Symptom to Meningitis</th>
<th>Worst CSF Findings, WBC/mm³</th>
<th>Diagnosis a</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Primary Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haiglip and O’Neil, 1931</td>
<td>M/45 y</td>
<td>Night watchman</td>
<td>Rabbit or squirrel</td>
<td>5</td>
<td>2100 (70% PMN)</td>
<td>Bacterial isolation: blood</td>
<td>None</td>
<td>Death</td>
<td>UG</td>
</tr>
<tr>
<td>Bryant and Hirsch, 1931</td>
<td>M/48 y</td>
<td>Chef</td>
<td>Rabbit</td>
<td>8</td>
<td>400 (84% M) G (75 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>None</td>
<td>Death</td>
<td>UG</td>
</tr>
<tr>
<td>Hartman, 1932</td>
<td>M</td>
<td>Butcher</td>
<td>Rabbit</td>
<td>9</td>
<td>145 G (42 mg/dL) 220</td>
<td>Serology</td>
<td>Blood transfusion from survivor of tularemia</td>
<td>Death</td>
<td>UG</td>
</tr>
<tr>
<td>Pund and Hatcher, 1937</td>
<td>F/12 y</td>
<td>None</td>
<td>Unknown</td>
<td>8</td>
<td>Serology</td>
<td>None</td>
<td>Death</td>
<td>OP</td>
<td></td>
</tr>
<tr>
<td>David and Owens, 1944</td>
<td>F/5 y</td>
<td>None</td>
<td>Cat</td>
<td>11</td>
<td>2000 (99% M) G (18 mg/dL)</td>
<td>Bacterial isolation: blood, CSF, T</td>
<td>Sulphathiazole blood transfusion from a recovered patient with tularemia</td>
<td>Death</td>
<td>UG</td>
</tr>
<tr>
<td>Stuart and Pullen, 1945</td>
<td>M/34 y</td>
<td>Unknown</td>
<td>Unknown</td>
<td>5</td>
<td>960 (100% M) G (45.4 mg/dL) P (643 mg/cm³)</td>
<td>Bacterial isolation: blood</td>
<td>None</td>
<td>Death</td>
<td>T</td>
</tr>
<tr>
<td>Fields, 1949</td>
<td>F/16 y</td>
<td>Unknown</td>
<td>Skinning rabbit</td>
<td>155</td>
<td>330 (70% M) G (26 mg/dL) P (730 mg/cm³)</td>
<td>Bacterial isolation: blood</td>
<td>Antitularemia horse serum intrathecally and intravenously</td>
<td>Recovered with sequelae</td>
<td>UG</td>
</tr>
<tr>
<td>Hutton and Everett, 1965</td>
<td>M/60 y</td>
<td>Unknown</td>
<td>Tick</td>
<td>9</td>
<td>2620 (63% PMN) G (39 mg/dL) P (174 mg/dL)</td>
<td>Serology</td>
<td>Chloramphenicol, streptomycin</td>
<td>Recovered</td>
<td>T</td>
</tr>
<tr>
<td>Lovell et al, 1986</td>
<td>M/13 mo</td>
<td>None</td>
<td>Cat scratch</td>
<td>59</td>
<td>13 200 (100% M)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol</td>
<td>Recovered</td>
<td>OP</td>
</tr>
<tr>
<td>Harper et al, 1986</td>
<td>M/18 mo</td>
<td>None</td>
<td>Unknown</td>
<td>8</td>
<td>3470 (96% M) G (53 mg/dL) P (205 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol</td>
<td>Recovered</td>
<td>OP</td>
</tr>
<tr>
<td>Hill et al, 1990</td>
<td>M/64 y</td>
<td>Unknown</td>
<td>Unknown</td>
<td>7</td>
<td>290 (60% M) G (32 mg/dL) P (350 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol, streptomycin, gentamicin</td>
<td>Recovered</td>
<td>T</td>
</tr>
<tr>
<td>Alles and Ayers, 1990</td>
<td>M/19 y</td>
<td>Construction</td>
<td>Rabbit</td>
<td>7</td>
<td>2127 (100%) G (30 mg/dL) P (115 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol, chloramphenicol</td>
<td>Recovered</td>
<td>OP</td>
</tr>
<tr>
<td>Pittman, 1996</td>
<td>M/5 y</td>
<td>None</td>
<td>Rabbit</td>
<td>3</td>
<td>Shunt fluid</td>
<td>7S (90%) G (59 mg/dL) P (23 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol, streptomycin followed by tetracycline</td>
<td>Recovered</td>
</tr>
<tr>
<td>Rodgers et al, 1998</td>
<td>F/4 y</td>
<td>None</td>
<td>Unknown</td>
<td>9</td>
<td>1570 (66%) G (34 mg/dL) P (120 mg/dL) 2 (62%) G (25 mg/dL) P (48 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Gentamicin, doxycycline</td>
<td>Recovered</td>
<td>UG</td>
</tr>
<tr>
<td>Weiner et al, 2004</td>
<td>M/17 mo</td>
<td>None</td>
<td>Tick</td>
<td>Unknown</td>
<td></td>
<td>Bacterial isolation: blood</td>
<td>Ceftriaxone</td>
<td>Death</td>
<td>UG</td>
</tr>
<tr>
<td>Gangt, 2007</td>
<td>F/51 y</td>
<td>Unknown</td>
<td>Rabbit</td>
<td>30</td>
<td>2926 (94% PMN) G (33 mg/dL) P (1000 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Streptomycin, doxycycline</td>
<td>Recovered with sequelae</td>
<td>T</td>
</tr>
<tr>
<td>Present study</td>
<td>M/21 y</td>
<td>Landscaper</td>
<td>Rabbit</td>
<td>7</td>
<td>1416 (73%) G (41 mg/dL) P (286 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol</td>
<td>Recovered</td>
<td>T</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; G, glucose; L, lymphocyte; M, monocyte; OP, oropharyngeal; P, protein; PMN, polymorphonuclear cell; T, typhoidal; UG, ulceroglandular; WBC, white blood cell.

a Serology indicates serum agglutination or CSF agglutination.
F *tularensis* usually requires a biosafety level 3 laboratory to protect laboratory personnel. Diagnosis of *F tularensis* DNA by means of polymerase chain reaction assay is also available for the diagnosis of tularemia; however, blood may contain compounds capable of inhibiting the assay.

Because of the difficulties in cultivating or directly detecting the bacteria, most cases of tularemia are diagnosed by demonstrating a diagnostic rise in serum antibodies to *F tularensis*. Antibodies to *F tularensis* can be detected approximately 2 weeks after the onset of symptoms. Latex agglutination, microagglutination, hemaggglutination, and enzyme-linked immunosorbent assay tests are commercially available. A polymerase chain reaction on tissue specimens has been developed but is not widely available. Real-time polymerase chain reactions on samples other than tissue are currently under investigation. Due to the time delays in establishing a firm diagnosis, the decision to treat in many patients has to be made on clinical suspicion. In our patient, no acute serologic testing was performed because the patient's CSF culture was positive for *F tularensis*, but the convalescent antibody titer at 8 months was 1:1024 by means of microagglutination testing.

Treatment for tularemic meningitis differs from the usual antibiotics given for bacterial meningitis. Ceftriaxone and other β-lactam antibiotics commonly used for empirical treatment of meningitis may be ineffective, as was the case in our patient. For tularemic meningitis, chloramphenicol and streptomycin is the regimen of choice. Genta- micin sulfate is an alternative if streptomycin is not available, but some studies suggest higher relapse rates for patients with tularemia who are treated with gentamicin vs streptomycin. Gentamicin was used in 2 of 17 patients with tularemic meningitis with successful treatment. Chloramphenicol was used in 7 of the 17 patients who were treated successfully; however, it should be used in conjunction with an aminoglycoside. Chloramphenicol is bacteriostatic and aminoglycosides are bactericidal, and the use of streptomycin, in particular, has been associated with lower relapse rates. Doxycycline has successfully cured tularemia meningitis in combination with an aminoglycoside and is effective in the treatment of tularemia in animal models. Ciprofloxacin has also been shown to treat tularemia in animal models, and has successfully treated 2 cases of human tularemia without meningitis. In the cases summarized in the Table, tularemia meningitis was most often successfully treated with streptomycin and chloramphenicol for 7 to 21 days.

In conclusion, our patient is typical in that he had recently worked as a professional landscaper performing high-risk activities that included mowing, brush cutting, and using a blower. He is also typical in that his diagnosis was delayed and he had poor response to empirical meningitis treatment with intravenous ceftriaxone. It is unknown whether the asymptomatic Chiari type 1 malformation noted on magnetic resonance imaging in our patient had any role in allowing *F tularensis* to enter the meninges from the bloodstream.

The outcome of tularemia meningitis is good if the diagnosis is made early, the correct antibiotics are given, and the patient does not have overwhelming bacterial sepsis or organ failure. Deaths have occurred in the patient series from misdiagnosis, use of inappropriate antibiotics, and occurrence during the era before antibiotics.

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