Francisella tularensis Endocarditis

Francisella tularensis, the agent of tularemia, is a widely distributed and extremely virulent gram-negative coccobacillus that induces disease in both human and animal hosts. Transmission of F. tularensis usually occurs by way of an arthropod vector or by direct animal contact; however, infection may also occur through aerosol inhalation, contamination of ocular or oral mucous membranes, or ingestion of bacteria. The manifestations of tularemia are protean and are classified into 6 syndromes: ulceroglandular, glandular, oculoglandular, pharyngeal, typhoidal, and pneumatic. Rare but reported manifestations include pericarditis and meningitis [1]. It is suspected that many cases go undiagnosed because of the often confusing presentations, the lack of clear exposure history, and the rarity of culture growth. To our knowledge, we describe the first documented case of F. tularensis endocarditis in a human host.

A 42-year-old man presented with a 2- to 3-day history of fever, chills, nonproductive cough, and pain on the left side of his chest. His medical history was remarkable only for cocaine and alcohol abuse. He denied iv drug use.

At admission, he had a temperature of 39.8°C, pulse rate of 101, respiratory rate of 20, and blood pressure of 138/84 mm Hg. Physical examination demonstrated no cervical, axillary, or inguinal adenopathy. Lung examination revealed markedly decreased airflow to the left base and midlung with bronchial breath sounds and sparse crackles. A grade 2/6 systolic murmur was detected at the left lower sternal border of the fifth intercostal space. This murmur was not present during prior documented examinations.

Initial laboratory studies showed a WBC count of 12.3 × 10^9/L, hemoglobin level of 14.0 g/mL, hematocrit of 41.2%, and platelet count of 90 × 10^9/L. Urine analysis showed 3+ blood, 2+ ketones, 3+ protein, 16–18 RBCs, and 8–10 granular casts per high-power field. Further laboratory studies disclosed the following values: sodium, 125 mEq/mL; potassium, 3.1 mEq/mL; chloride, 86 mEq/mL; CO2, 30.2 mEq/mL; blood urea nitrogen, 9 mg/dL; creatinine, 1.3 mg/dL; lactate dehydrogenase, 113 U/L; and alanine aminotransferase, 42 U/L. Serology for HIV was negative. Chest radiography showed previously described findings of bilateral emphysematous changes with bullae. A new poorly defined density without calcification or cavity was found in the left midlung.

He was admitted to the general medicine service with a presumptive diagnosis of community-acquired pneumonia. After blood specimens for culture were obtained, a therapeutic regimen of cefotetan and erythromycin was initiated. He remained febrile with no clinical improvement through the fourth hospital day, at which time a precordial echocardiogram indicated the presence of a mitral valve vegetation. On the morning of the fifth hospital day, his condition progressed to respiratory failure, requiring emergent intubation and ventilatory support. Chest radiography now revealed the presence of diffuse airspace disease in the right lung, densely consolidated pneumonia in the midzone of the left lung, and a left pleural effusion. His antibiotic regimen at this time included vancomycin, piperacillin/tazobactam, erythromycin, and gentamicin for coverage of potential pathogens of both typical and atypical pneumonia and endocarditis.

A transesophageal echocardiogram indicated the presence of a mobile echodensity on the anterior leaflet of the mitral valve that was suspicious for a vegetation. Bronchoscopy was performed; gram staining, acid-fast staining, and fungal staining of bronchial material were negative, as were findings of direct fluorescent antibody testing for Legionella. Initial serological studies for F. tularensis, Coxiella burnetii, Mycoplasma, and Brucella were negative. On the ninth hospital day, culture of blood obtained at the time of admission was determined to be positive by the BACTEC System (Becton Dickinson, Sparks, MD). Subculture growth on chocolate agar revealed pleomorphic gram-negative rods subsequently identified by the Arkansas State Laboratory (Little Rock) as F. tularensis. Titers of antibody to F. tularensis determined after 1 and 2 weeks of hospitalization were 1 : 80 and 1 : 800, respectively.

The patient’s condition progressively improved with subsequent extubation. After positive results of blood culture were obtained, antibiotic therapy was changed to gentamicin and ciprofloxacin. Ciprofloxacin treatment was discontinued after identification of F. tularensis, and a 4-week course of gentamicin therapy was completed. After completion of antibiotic therapy, the patient appeared to have responded well; however, he did not return for follow-up evaluation.

Although not consistent with the current diagnostic criteria for endocarditis [2], a positive blood culture in the presence of a new murmur and an echocardiography-detected vegetation with otherwise consistent clinical features strongly suggests that F. tularensis caused endocarditis in this case. To our knowledge, F. tularensis endocarditis has not been previously reported in the medical literature, which may be due to the extreme difficulty of obtaining positive blood cultures in the presence of criteria suggesting endocarditis.

Isolation of F. tularensis via blood culture is exceedingly rare, and this bacterium usually is detected by radiometric blood culture systems (such as the BACTEC System) [3]. It is noteworthy that in our case, the identification of F. tularensis as a blood-borne pathogen would have been impossible if it had not been requested that the blood cultures be incubated for an extended period for the identification of fastidious bacteria. F. tularensis is a fastidious organism that grows poorly, if at all, on standard culture media. The use of chocolate agar, a nu-

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tritionally diverse media containing cysteine, facilitated the growth of the bacteria and led to a rapid and confirmatory diagnosis that would have been delayed by serology alone.

Successful treatment of our patient consisted of 4 weeks of iv gentamicin. Gentamicin is considered an acceptable alternative to streptomycin and is preferable for prolonged courses of therapy where intramuscular injections would be impractical. Our patient demonstrated no signs of gentamicin-related toxicity during the course of his therapy. Most certainly, his age and underlying good health contributed to this outcome. Quinolones have been used to successfully treat pneumonic and ulceroglandular tularemia. Chloramphenicol and tetracyclines have been used successfully in the treatment of tularemia; however, the efficacy of these agents in the setting of endocarditis is unknown since they are both bacteriostatic. Cephalosporins have demonstrated no clinical efficacy against *F. tularensis*, despite in vitro data often exhibiting favorable MICs [4].

*F. tularensis* endocarditis should be considered in undetermined cases that are clinically and epidemiologically suggestive of tularemia. Efforts should be made to isolate the blood-borne pathogen through appropriate laboratory and culture techniques, and empirical therapy should include gentamicin.

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References

Trofloxacin-Induced Acute Hepatitis

Trofloxacin, a new trifenamophyridone derivative related to fluoroquinolone antimicrobial drugs, appears to be more effective than available quinolones. As a class, the most common adverse effects involve the CNS and gastrointestinal tract [1]. Liver enzyme abnormalities have been noted in 2%–3% of patients, and liver toxicity is reported infrequently [2]. Since use of this drug in the United States was authorized in December 1997, 152 cases of serious hepatic events probably related to trofloxacin have been reported to the US Food and Drug Administration (140 cases) and to the European Agency for the Evaluation of Medicinal Products (12 cases as of July 1998). Because the frequency of serious adverse reactions to trofloxacin was well out of proportion to that seen in other drugs in this class, the manufacturer withdrew trofloxacin from the European markets on 15 June 1999. The drug remains available in the United States for very restricted indications [3]. We report 3 patients who had acute hepatitis after taking trofloxacin.

A 68-year-old man (patient 1) was treated with trofloxacin (200 mg/d) for 7 days because of a flulike syndrome. Ten days after treatment ended, he noticed fever and dark urine. He was prescribed roxithromycin, paracetamol, and carbocisteine. On admission 5 days later, he was febrile (40°C) and jaundiced. Laboratory results indicated hepatocellular injury without evidence of viral causes (table 1). Screening for autoantibodies was negative. Findings of an abdominal ultrasonographic examination were normal. A liver biopsy specimen showed predominantly centrozonal necrosis and inflammatory eosinophilic infiltrates. Laboratory findings at 45 days were normal.

A 33-year-old man (patient 2) was treated with trofloxacin (200 mg/d) for 7 days because of a flulike syndrome. Ten days after treatment ended, he noticed fever and dark urine. He was prescribed roxithromycin, paracetamol, and carbocisteine. On admission 5 days later, he was febrile (40°C) and jaundiced. Laboratory results indicated hepatocellular injury without evidence of viral causes (table 1). Screening for autoantibodies was negative. Findings of an abdominal ultrasonographic examination were normal. A liver biopsy showed marked centrozonal necrosis and eosinophilic infiltrates. Laboratory findings at 45 days were normal.

<table>
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<th>Patient</th>
<th>Total AST, U/L</th>
<th>Direct AST, U/L</th>
<th>Total ALT, U/L</th>
<th>Direct ALT, U/L</th>
<th>Total AP, U/L</th>
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NOTE. ALT, alanine aminotransferase (normal, ≤40 U/L); AP, alkaline phosphatase; AST, aspartate aminotransferase (normal, ≤35 U/L); normal total bilirubin, <17.1 μmol/L.

* Values in parentheses are multiples of upper limit of normal.