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Case Report

CASE REPORT

Francisella tularensis bacteraemia causing multi-organ failure

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Abstract

Tularemia is a zoonosis caused by the gram-negative coccobacillus *Francisella tularensis*. The bacterium can be transmitted in several ways including direct contact with animal reservoirs, ingestion, inhalation and bites, and typical clinical symptoms are headache, fever, diarrhea and dyspnea. *Francisella tularensis* has two predominant subspecies (ssp), namely ssp. *tularensis* and ssp. *holarctica*. Ssp. *holarctica* is less virulent and does usually not cause fatal disease. We here present a 51-year-old male with sepsis and multi-organ failure caused by *F. tularensis* ssp. *holarctica* infection suggesting that atypical agents including *F. tularensis* should be considered in patients presenting symptoms of infections without response to standard treatments.

INTRODUCTION

Tularemia is a rare zoonotic disease caused by the gram-negative coccobacillus *Francisella tularensis*. It is mainly transmitted by direct contact with animal reservoirs, ingestion, inhalation, contaminated water or tick bites. Clinical manifestations and treatment outcomes differ between subspecies. In Europe, the *F. tularensis* subspecies (ssp.) *holarctica* is most frequently associated with human disease and typically causes mild clinical symptoms. However, the pathogen is rarely isolated in Norway. We here present a case of multi-organ failure due to *F. tularensis* infection in a patient with alcoholic liver cirrhosis.

CASE REPORT

A 51-year-old male living in a rural part of western Norway was hospitalized after 2 weeks of influenza-like symptoms including fever, mild headache and a reduced general condition. During the last week before hospitalization, his wife had noted abdominal distention. Otherwise, no focal symptoms were noted. Two days prior to admittance, he started oral penicillin because of bacterial sinusitis. Previous medical history was significant for alcohol abuse, pancreatitis and alcoholic liver cirrhosis.

At admittance, he had memory and orientation impairment. Physical examination revealed blood pressure 133/85 mmHg, heart rate 107 beats per minute, temperature 40.3°C, respiratory rate 24 per minute and oxygen saturation 97%. He had scleral icterus and the abdomen was significantly distended although he denied abdominal pain. Laboratory tests showed leukocytes 8.8×10^9/l (references: $4.3–10 \times 10^9$/l), platelet count 26×10^9/l (references: $145–348 \times 10^9$/l), hemoglobin 13.8 g/dl (references: 13.4–17.0 g/dl), international normalized ratio (INR) 1.1 (references: <1.1), activated partial thromboplastin time 41 s (references: 28–48 s), sodium 133 mmol/l (references: 137–145 mmol/l), potassium 3.2 mmol/l (references: 3.5–5.0 mmol/l), magnesium 0.56 mmol/l (references: 0.71–0.94 mmol/l), creatinine 58 μmol/l (references: 60–105 μmol/l), alanine aminotransferase 59 U/l

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(references: <70 U/l), alkaline phosphatase 171 U/l (references: <105 U/l), C-reactive protein (CRP) 123 mg/l (references: <5 mg/l), gamma glutamyl transferase 2016 U/l (references: <115 U/l), amylase 59 U/l (references: >120 U/l), bilirubin 42 μmol/l (references: 5–25 μmo/l). Screening for human immunodeficiency virus, hepatitis B and C antibodies were all negative and serum antinuclear antibodies and antineutrophil cytoplasmic antibodies were not detected. Computer tomography (CT) of the skull and brain revealed signs of sinusitis. Ultrasound of the liver was consistent with cirrhosis and ascites. Blood cultures were taken before cefotaxime was prescribed for his sinusitis and a potential spontaneous bacterial peritonitis. In addition, he was given thiamine prophylaxis against Wernicke's encephalopathy.

Over the next 6 days, he developed decompensated liver failure, CRP increased to 200 mg/l, bilirubin to 159 μmol/l and INR to 1.5. Microbiological cultures were negative. A systemic autoimmune condition was considered unlikely because of negative immunological tests. He was persistently febrile, confused and developed an increasing oxygen demand. A CT scan of his thorax and abdomen showed bilateral pneumonia and right-sided pleural effusion. Thoracentesis revealed one liter of bloody pleural fluid and a bronchoscopy including a bronchial alveolar lavage (BAL) was performed. Because of liver cirrhosis, he was considered to be at risk for infections with atypical and opportunistic microbes. However, BAL polymerase chain reaction (PCR) was negative for *Pneumocystis jiroveci* and *Legionella pneumophila*. Blood cultures were repeated and incubated for an extended time period together with samples from the pleural effusions. The antibiotics were changed to meropenem and ciprofloxacin to better cover gram negative and intracellular microbes. Additionally, fluconazole was added to provide coverage for the possibility of infection with *Candida* species. However, his condition did not improve and he developed progressive multi-organ failure and increasing encephalopathy. Due to poor compliance and ongoing alcohol abuse, he was not considered to be a candidate for liver transplantation. Death occurred 12 days after admittance.

On the following day, there was growth of gram-negative coccobacilli on the chocolate agar from the pleural fluid specimen and later also in the blood cultures, after incubation for 5 and 8 days, respectively. The isolates were identified as *F. tularensis* by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Maldi-Tof MS, Bruker Daltonics, Bremen). Species identity was later confirmed by real-time PCR at The Norwegian National Reference Laboratory as *F. tularensis* non-subspecies *tularensis*, although exact subspecies was not identified.

DISCUSSION

Francisella tularensis is an aerobic, gram-negative coccobacillus causing tularemia, a zoonotic infection primarily observed in the Northern Hemisphere [1]. The bacterium can be transmitted via direct contact with infected animals, arthropod bites, and by ingestion or inhalation. Rodents like hares and rabbits, mosquitoes and ticks are typically reservoirs. Contaminated water or soil may cause human infections [2] and also laboratory-acquired tularemia has been reported [3]. In our case, the source of infection was most likely the patient's private well for drinking water, which according to his familiy was contaminated with surface water.

Table 1: An overview of the clinical types of Tularemia [5, 6].

Form	Route of acquisition
Ulceroglandular or glandular	Vectorborne or touching material or animals infected with *F. tularensis*
Oculoglandular	Contaminated material on the eye (from fingers or infected dust)
Oropharyngeal	Ingesting infected food or water
Respiratory	Inhaling contaminated dust or as a secondary manifestation from the oropharyngeal or typhoidal form
Typhoidal	Unknown

Typically, two ssp. of *F. tularensis* are dominating in human infections. *F. tularensis* ssp. *tularensis (type A)* strains are mainly found in Canada and USA and *F. tularensis* ssp. *holarctica (type B)* strains are found throughout the Northern Hemisphere, including Europe [4]. The ssp. *tularensis* can cause severe invasive diseases such as pneumonia and bacteremia whereas ssp. *holarctica* usually causes mild symptoms and have a low mortality rate (0.99%) [2, 4]. Tularemia is a rare disorder in the western parts of Norway with only 78 cases reported over the last 40 years, only 15 from our region [5]. Our patient probably suffered from *F. tularensis* ssp. *holarctica* since ssp. *tularensis* was excluded with the PCR assay. Although not performed in our case, a subspecies specific PCR analysis targeting the region of difference-1 (RD1) could probably identify the exact subspecies.

Tularemia can present with a variety of clinical symptoms and six different clinical forms are described (Table 1) [6, 7]. In our case report the patient developed multi-organ failure with pneumonia and bacteremia. Bacteremia is associated with underlying conditions such as diabetes mellitus, high age, alcohol abuse and immunosuppression [8]. Isolation of *F. tularensis* in blood culture is exceedingly rare and has only been reported infrequently in Europe [8]. However, our isolation of the strain was probably due to prolonged bacteremia in the patient as well as an extended incubation period of the samples.

First line treatment for severe *F. tularensis*, which requires hospitalization, is parenteral administration of an aminoglycoside. Aminoglycosides usually display a low minimal inhibitory concentration, have a bactericidal effect and a lower treatment failure rate compared to doxycycline [9]. In less severe cases fluoroquinolones, doxycycline and chloramphenicol are suggested [10, 11]. Notably, *F. tularensis* is resistant to all betalactam-antibiotics including the carbapenems. Initially, we did not suspect tularemia in our patient and adequate antimicrobial treatment was therefore delayed. Aminoglycosides was anyhow not given to our patient because of crucial contraindications.

CONCLUSION

We here report a patient presenting severe sepsis and multi-organ failure caused by the low virulence *F. tularensis*. We therefore suggest that tularemia should be considered in patients at risk of infection with atypical microbes not responding to regular treatment. A high index of suspicion is needed to establish the correct diagnosis and prolonged incubation of blood cultures and microbiological samples should be considered for detection of fastidious bacteria.

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CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

No approval is required.

CONSENT

The patient's relatives gave written informed consent for publication of this case report.

GUARANTOR

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