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CASE REPORT

Tularemia in the Southeastern Swiss Alps at 1,700 m above sea level

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Abstract A 37-year-old man presented with a 4-day history of nonbloody diarrhea, fever, chills, productive cough, vomiting, and more recent sore throat. He worked for the municipality in a village in the Swiss Alps near St. Moritz. Examination showed fever (40 °C), hypotension, tachycardia, tachypnea, decreased oxygen saturation (90 % at room air), and bibasilar crackles and wheezing. Chest radiography and computed tomography scan showed an infiltrate in the left upper lung lobe. He responded to empiric therapy with imipenem for 5 days. After the imipenem was stopped, the bacteriology laboratory reported that 2/2 blood cultures showed growth of *Francisella tularensis*. He had recurrence of fever and diarrhea. He was treated with ciprofloxacin (500 mg twice daily, oral, for 14 days) and symptoms resolved. Further testing confirmed that the isolate was *F. tularensis* (subspecies *holarctica*) belonging to the subclade B.FTNF002-00 (Western European cluster). This case may alert physicians that tularemia may occur in high-altitude regions such as the Swiss Alps.

Keywords *Francisella tularensis* · Infection · Pulmonary · Switzerland · Altitude

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Case report

A 37-year-old man presented with a 4-day history of nonbloody diarrhea, fever, chills, productive cough, vomiting, and more recent sore throat. He worked for the municipality in a village in the Swiss Alps near St. Moritz, which is situated in a valley at 1,700 m above sea level. He did not leave the local area during the previous 3 months. He did not eat any raw meat or milk. He had no close contact with domestic or wild animals, and he did not notice any tick bites. Past medical history included compensated congenital chronic hepatitis B infection. He had emigrated from Ethiopia to Switzerland 17 years ago, smoked 30 cigarettes per day, and had a history of chronic alcoholism that was treated with disulfiram for the previous 1.5 years.

Examination showed fever (40 °C), hypotension (80/60 mmHg), tachycardia (100 beats/min), tachypnea (20 breaths/min), decreased oxygen saturation (90 % on room air), and bibasilar crackles and wheezing. The abdomen was soft and had active bowel sounds. Skin examination and cardiac auscultation were normal. Laboratory studies showed white blood cell count 2.1×10^9/L (reference range, 3.0–9.0 $\times 10^9$/L), neutrophils 1.29×10^9/L (reference range, 1.4–8.0 $\times 10^9$/L), thrombocytes 69×10^9/L (reference range, 150–400 $\times 10^9$/L), C-reactive protein 125 mg/L (reference range, <5 mg/L), alanine aminotransferase 77 U/L (reference range, <41 U/L), and aspartate aminotransferase 200 U/L (reference range, <40 U/L); the alanine and aspartate aminotransferase levels had been normal 2 weeks earlier. The human immunodeficiency virus and hepatitis C serology were negative. Urinalysis and abdominal ultrasonography were normal. Chest radiography showed marginal infiltrates in the left upper lung lobe. Chest computed tomography scan

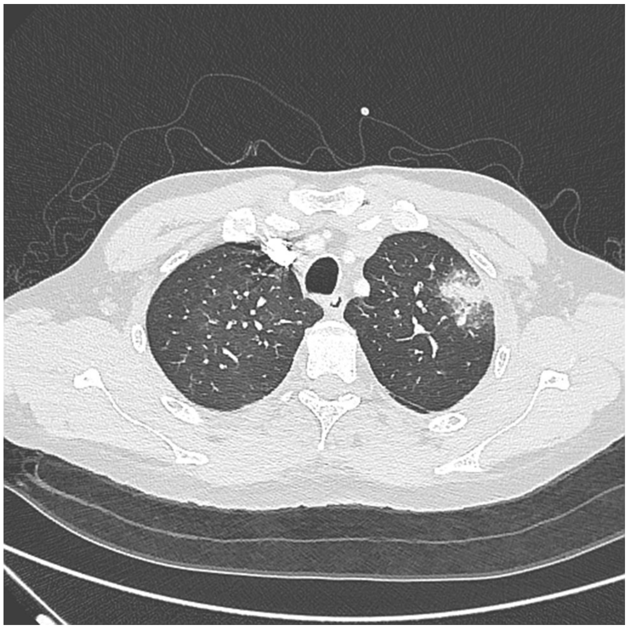

Fig. 1 A 37-year-old man who had diarrhea, fever, chills, cough, vomiting, and sore throat. Chest computed tomography scan showed an infiltrate in the left upper lung lobe

showed an infiltrate in the left upper lung lobe, enlarged lymph nodes in the left hilum, and normal upper liver, spleen, and adrenal glands (Fig. 1). Cytologic examination of bronchial brush biopsies showed inflammatory cells (mostly neutrophilic granulocytes) without malignancy.

The patient received empiric broad spectrum therapy with imipenem (2 g/d, intravenous). On day 5, all symptoms resolved, imipenem was stopped, and preliminary results of blood and stool cultures showed no bacterial growth. On day 7, the patient was asymptomatic and discharged from the hospital. At 2 days after discharge, the bacteriology laboratory reported that 2/2 blood cultures showed growth of *Francisella tularensis* after 7 days in the laboratory (minimal inhibitory concentration for ciprofloxacin, 0.032 mg/L). The patient was called by telephone and he reported recurrence of fever and diarrhea. He was started on ciprofloxacin (500 mg twice daily, oral, for 14 days), and symptoms resolved.

The isolate was further confirmed as *F. tularensis* (subspecies *holarctica*) by polymerase chain reaction tests that targeted the *fopA* gene and the region of difference one [1]. A supplementary polymerase chain reaction test that targeted the region of difference 23 identified the isolate as belonging to the subclade B.FTNF002-00 (Western European cluster) [1]. Sequence analysis of the single nucleotide polymorphism markers B.18 (derived state) and B.19 (ancestral state) confirmed the subclade B.FTNF002-00, which is endemic in Switzerland and Western Europe [2, 3]. In addition, the multiple-loci variable number of tandem repeats analysis profile corresponded to the profile of strains circulating in Western Europe and Switzerland (Fig. 2) [2–4].

Discussion

Tularemia is a rare but potentially severe zoonosis that is endemic in the northern hemisphere. It is caused by the Gram-negative coccobacillus *F. tularensis*, which initially was isolated in 1912 [5–7]. *F. tularensis* comprises three subspecies. The clinically relevant subspecies include subspecies *tularensis* (genotypes A1a, A1b, and A2) and subspecies *holarctica* (genotype B) and have different virulence and frequency of mortality [A1a, 4 %; A1b, 24 %; A2, 0 %; B, 7 %; (United States, 1964–2004)]. In Europe, only subspecies *holarctica* has been identified [8].

In humans, tularemia can cause several disease patterns, depending on the site of entry into the body. The most common form of the disease is ulceroglandular tularemia, which usually is caused by a bite from an infected arthropod vector or direct contact with a contaminated source [6]. After an incubation period (typically 3–6 days), the patient experiences a sudden onset of flu-like symptoms, especially chills, fever, headache, and generalized aches. Furthermore, ulceroglandular tularemia may present with an ulcer that may persist for several months. Glandular tularemia is a disease that has similar symptoms as ulceroglandular tularemia but without the appearance of an ulcer [7]. Oculoglandular tularemia may occur more rarely, and the bacterium is acquired by direct contamination of the conjunctiva [9].

The ingestion of infected foods or contaminated drinking water may cause oropharyngeal or gastrointestinal tularemia, depending on the site of colonization in host tissues [10]. Oropharyngeal tularemia may be associated with painful sore throat, enlargement of the tonsils, the formation of a yellow-white pseudomembrane, and swollen cervical lymph nodes [6]. Depending on the infecting dose, gastrointestinal tularemia may be mild and persistent or an acute fatal disease (typhoidal tularemia) associated with extensive bowel ulceration.

Primary pulmonary tularemia may be caused by the inhalation of bacteria, but most commonly may occur secondary to the septic spread of ulceroglandular, glandular, oculoglandular, or oropharyngeal tularemia [11]. The clinical and radiographic features of pulmonary tularemia are varied and the diagnosis may be difficult [11]. Pulmonary tularemia occasionally may occur without any overt signs of pneumonia. Inhalational tularemia may be caused by farming activities that involve the handling and generation of dust from hay that previously was the residence of infected rodents [6].

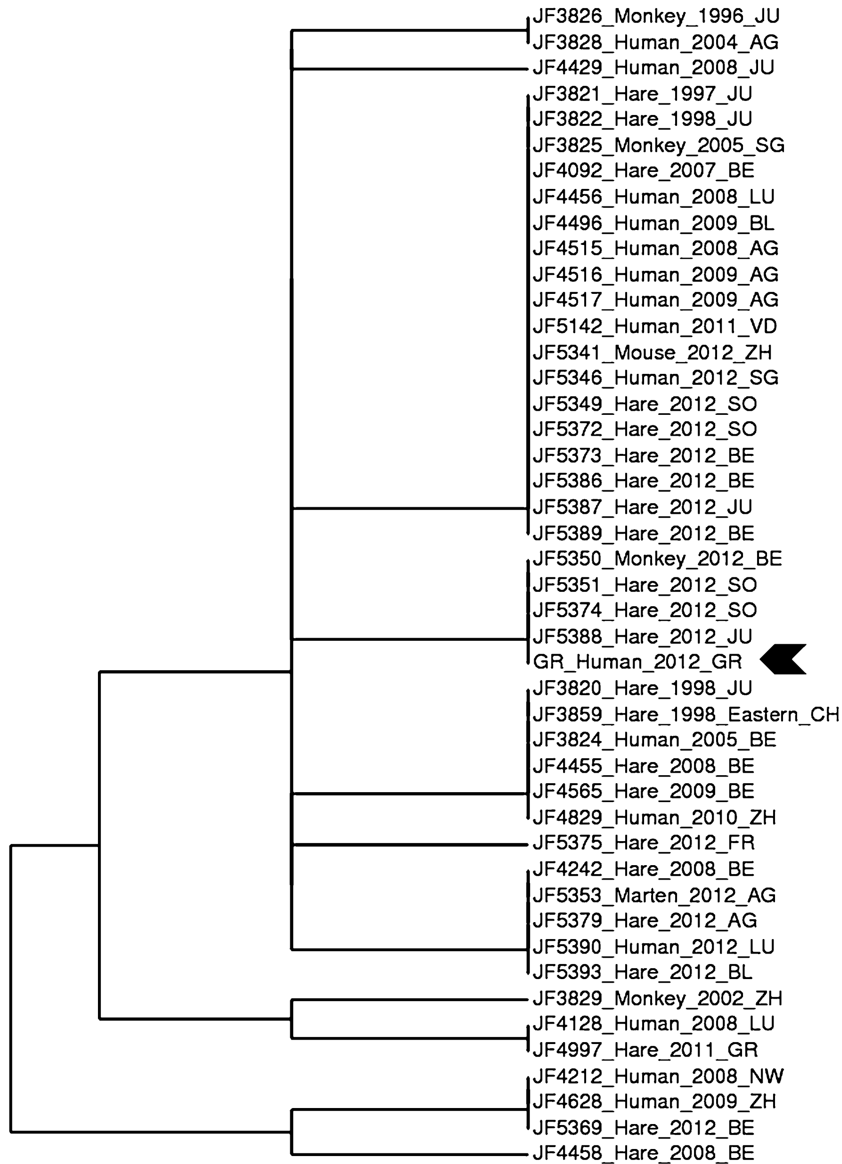

Fig. 2 Clustering dendrogram comparing Swiss strains of *Francisella tularensis* (subspecies *holarctica*) subclade B.FTNF002-00. Name of strain, host, year of isolation, and canton (Swiss state) are noted for each strain. The *arrowhead* shows the human strain isolated in Graubünden, Switzerland in 2012. This analysis was performed using six markers of multiple-loci variable number of tandem repeats analysis (Ft-M3, Ft-M6, Ft-M20, Ft-M21, Ft-M22, Ft-M24) and the program from the online software tool from the bank of multiple-loci variable number of tandem repeats analysis. The Newick string was imported into software (TreeDyn, GEMI Bioinformatics, Montpellier, France) and a dendrogram was drawn [4]. Abbreviations (Swiss cantons): *AG* Aargau, *BE* Bern, *BL* Basel Land, *FR* Freiburg, *GR* Graubünden, *JU* Jura, *LU* Luzern, *NW* Nidwald, *SG* Sankt-Gallen, *SO* Solothurn, *VD* Vaud, *ZH* Zürich

The diagnosis of tularemia may require a high index of clinical suspicion from the patient's presentation and epidemiologic factors. Diagnostic tests include serologic antibody test, direct polymerase chain reaction, and bacterial culture. Disadvantages of culture include the biological safety risk and risk of false negative results because of the fastidious growth requirements of the organism.

Effective antibiotic therapy for tularemia may include streptomycin, gentamicin, tetracyclines, chloramphenicol, and fluoroquinolones. Fluoroquinolones are highly effective against *F. tularensis* in vitro and have been used successfully to treat several patients in Europe that had the less virulent subspecies *holarctica*. In Europe, oral fluoroquinolones are the therapy of choice for mild-to-moderate disease because these drugs have fewer and less severe adverse events than aminoglycosides. However, fluoroquinolones may not be the treatment of choice in the United States because the virulence of strains may be greater in the United States than Europe [5, 12]. In the present patient, treatment with imipenem caused defervescence, even though *F. tularensis* subspecies *holarctica* may be resistant to imipenem [13]. This resistance may have caused the patient's relapse, which responded promptly to fluoroquinolone therapy. In pregnant women, ciprofloxacin and doxycycline are not approved by the United States Food and Drug Administration, and gentamicin or streptomycin may be recommended as alternative therapy [14].

Many hematophagous arthropod species worldwide, including ticks, tabanid flies (horseflies and deerflies), fleas, and mosquitoes, may transmit tularemia to mammalian hosts [15]. Arthropods such as ticks may be the principal vectors of transmission in North America, as shown in 56 of 81 patients in Missouri. The average annual incidence of tularemia in Missouri in 2000–2007 was 40 cases per 100,000 people, but it is much less frequent in Europe [5]. In Switzerland, tularemia occurs sporadically and had an incidence of 0.04 cases per 100,000 people in 2004 (total, three cases), but the incidence in 2012 was 0.5 cases per 100,000 people (total, 41 cases). Tularemia has been a mandatory reportable disease in Switzerland since 2004 and all diagnosed cases should be registered [16]. In the canton of Graubünden in southeastern Switzerland, three cases of tularemia have been reported, and the present case is the first known case of typhoidal tularemia [16]. Only two other cases of typhoidal tularemia in Switzerland have been reported to the Swiss Federal Office of Public Health since 2004, one each from the Luzern and Aargau cantons, both located approximately 400 m above sea level [16]. Literature search showed no reported case of tularemia at higher elevation in the Swiss Alps, especially higher than 1,700 m above sea level.

The Swiss Federal Institute of Health has reported an increase in the incidence of tularemia since 2007 in Switzerland [16]. This may be attributed to improved diagnostic laboratory testing including the more frequent use of polymerase chain reaction, cysteine-enriched media such as chocolate agar, and prolonged culture. In addition, climate change caused by global warming may improve growth conditions for the most common vectors and may increase the incidence of tularemia, as shown in studies from Scandinavia, the Russian arctic region, and Turkey [17–19]. Comparable effects may occur in Switzerland because of climate change in regions of high altitude above sea level. An increase in winter temperature may improve survival of animal or bird hosts and insect vectors that may transmit infectious agents. Increased number of hot summer days may be associated with increased activity of infected mosquitoes, horseflies, and ticks and associated human exposure to pathogens carried by these insects and ticks [18].

The present case was remarkable because the presenting complaint was diarrhea, with a later onset of sore throat. Therefore, this patient may have had primary gastrointestinal tularemia and secondary septicemia. In addition, the patient was a council worker and may have acquired the infection from his job, working the most time outdoors. Numerous animals may be carriers of *F. tularensis* in the Upper Engadin region of Switzerland (Table 1) [20]. The patient denied any animal contact or other common sources of infection. The presenting symptom of diarrhea suggests that he may have ingested infected food or contaminated water. He had not left the valley for a minimum 3 months, which exceeds the typical incubation time (3–6 days) [7]. Therefore, he must have acquired the infection in the Upper Engadin region. As a council worker, the patient had frequent contact with fresh water that may have been contaminated, and this may be the most plausible route of exposure for this patient.

Table 1 Rodent and Lagomorph species that may be infected by *Francisella tularensis* in the Canton of Graubünden, Switzerland at elevation >1,500 m (modified from [20])

Species	Common name
Lepus timidus	Mountain hare
Lepus europaeus	Brown hare
Sciurus vulgaris	Red squirrel
Marmota marmota	Alpine marmot
Eliomys quercinus	Garden dormouse
Dryomys nitedula	Forest dormouse
Muscardinus avellanarius	Common dormouse (hazel dormouse)
Apodemus sylvaticus	Wood mouse
Apodemus flavicollis	Yellow-necked mouse
Apodemus alpicola	Alpine field mouse
Mus domesticus	House mouse
Clethrionomys glareolus	Bank vole
Arvicola terrestris	Water vole
Microtus subterraneus	European pine vole
Microtus arvalis	Common vole
Chionomys nivalis	European snow vole

Based on review of the literature and public health information, this may be the first reported case of tularemia in a high valley in the Swiss Alps >1,700 m above sea level. Climate change may increase the incidence of cases at high elevation in the future. This case report may alert physicians that tularemia may occur in high-altitude regions such as the Swiss Alps.

Conflict of interest The authors certify that they have no actual or potential conflict of interest in relation to this article.

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