Skin involvement in *Francisella tularensis* infection: a case report of two clinical cases

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**Abstract**
Tularemia, or rabbit fever, is a zoonotic infection caused by *Francisella tularensis*, a Gram-negative cocccobacillus. *F. tularensis* subsp. *holarctica* (type B) is the predominant form in Slovenia. Humans become infected through arthropod bites, direct contact with an infected animal, ingestion of contaminated water or food, and inhalation of contaminated aerosol. The most common form is ulceroglandular tularemia (> 80%), which is characterized by a skin ulcer and regional lymphadenopathy. Below we present two cases of tularemia with skin involvement.

**Keywords:** tularemia, zoonotic infection, ulceroglandular form, oropharyngeal tularemia, treatment

**Introduction**

Tularemia, or rabbit fever, is a zoonotic infection caused by the Gram-negative bacterium *Francisella tularensis*, with *F. tularensis* subsp. *holarctica* (type B) being the most commonly detected subspecies in Slovenia (1–4). We record individual cases of tularemia every year in Slovenia, mostly limited to the Upper Carniola and Prekmurje regions (1, 5). In the summer of 2021, we recorded a major outbreak of tularemia in the Gorizia region. The cause was contaminated water in three private water mains (4). The most common form of tularemia is ulceroglandular tularemia, which accounts for more than 80% of all reported cases (6). The infection is confirmed by serological tests (agglutination test, enzyme-linked immunosorbent assay [ELISA]); diagnostic convalescent antibody titers do not appear until at least 2 to 4 weeks after the onset of symptoms (1–3). It is treated with aminoglycosides, tetracyclines, and fluoroquinolones (1–3). Below we present two clinical cases of tularemia with skin involvement.

**Case report 1**

A 76-year-old woman with known heart failure, chronic atrial fibrillation, arterial hypertension, and type 2 diabetes was hospitalized at the University Medical Center Maribor in September 2021. She was treated with the antibiotic cefuroxime for a suspected bacterial infection. During hospitalization she reported pain in her right ear and throat. She was examined by an otorhinolaryngologist, who found white plaque in the right tonsil area and enlarged, painful lymph nodes in levels II and III of the right cervical space. Due to the failure of cefuroxime therapy, she was subsequently treated with amoxicillin/clavulanic acid and metronidazole, but signs of right-sided tonsillitis and lymphadenitis persisted.

An ultrasound of the right side of her neck showed a conglomerate of lymph nodes 7 to 17 cm in size, all with disrupted architecture and mixed type of vascularization. A lymph node conglomerate was punctured, and purulent content was collected. Cytological examination of the lymph node sample showed exudative proliferative inflammation with granuloma formation and was negative for pathogenic bacteria and mycobacteria.

The patient was seen by an infectious disease specialist in September 2021. During the examination she reported general weakness and enlarged lymph nodes on the right side of her neck with yellowish-white purulent discharge. Laboratory results showed leukocytosis (10.79 × 10^9/l), mildly elevated C-reactive protein (39 mg/l), and liver enzymes (AST 0.54 μkat/l, ALT 0.69 μkat/l, and gamma-GT 1.54 μkat/l). The patient reported having two sheep at home but denied being bitten by a tick or other insect. Serology was performed for *Brucella* spp., *Coxiella burnetii*, and *F. tularensis*. A diagnosis of tularemia was confirmed by ELISA, which showed high antibody titers (*F. tularensis* IgM reactive > 1: 256, IgG reactive > 1: 256). Doxycycline 100 mg bid for 21 days was prescribed. After completing antibiotic therapy, the patient reported improvement in her general condition. Clinically, the cervical lymph nodes on the right side were still enlarged with purulent discharge (Fig. 1).
F. tularensis was also confirmed by polymerase chain reaction (PCR) on the discharge. Due to insufficient improvement, antibiotic therapy was switched, and treatment continued with ciprofloxacin 500 mg bid for 14 days. At the last follow-up examination, the lymph nodes were significantly smaller, there was no more discharge, and the patient’s general condition had improved; a small scar formed at the site of the fistula.

Case report 2

A 69-year-old female patient with no comorbidities visited the infectious diseases clinic in September 2021 due to a fever of up to 38 °C, chills, myalgia, abdominal pain, and headache. She was feeling nauseous, had diarrhea, and had lost her appetite. She denied being in contact with animals, recently traveling, or swimming in lakes. She reported having multiple ticks 2 weeks earlier. Approximately a week after a tick bite, she noticed redness at the site of the bite, which expanded from her armpit to chest. She had already been treated with the antibiotic amoxicillin/clavulanic acid 1,000 mg bid, which was prescribed to her 2 days earlier at the emergency department because of suspected cellulitis. Upon examination the abdomen was soft but tender to the touch. Laboratory results showed lymphocytopenia (0.84 x 10^9/l), elevated C-reactive protein (123 mg/l), mildly elevated liver enzymes (ALT 0.71 μkat/l), and mildly elevated lactate dehydrogenase (LDH; 4.78 μkat/l). Because of suspected anaplasmosis doxycycline 100 mg bid was prescribed for 7 days. After completing antibiotic therapy, the patient reported only partial improvement of the symptoms; the fever and chills were gone. She was still complaining of myalgia, fatigue, malaise, and loss of appetite. She developed a black eschar that had developed at the site of the tick bite. Serologies for Anaplasma phagocytophilum, Leptospira spp., hantaviruses, and F. tularensis were negative. PCR of skin lesions for F. tularensis and Leishmania spp. were negative. Four weeks later she was still complaining of myalgia, fatigue, and malaise. The black eschar that had developed at the site of the tick bite had fallen off. Underneath there was a yellow ulcer with no discharge or signs of secondary bacterial infection. The ulcer was painful with pain spreading to the right side of the chest. The axillary lymph nodes were not palpable (Fig. 2).

Laboratory results showed elevated sedimentation rate (SR; 52 mm/h) and mildly elevated C-reactive protein (7 mg/l). Three weeks after the negative serology test for F. tularensis, we repeated it, and it was positive (IgG reactive > 1:256 and IgM reactive > 1:256). F. tularensis was also confirmed using PCR from a skin biopsy from the ulcer area. Antibiotic therapy with doxycycline 100 mg bid for 21 days was prescribed. After completing antibiotic therapy, she reported partial improvement of her condition; the myalgia, abdominal pain, and fatigue were gone. Her appetite had returned. An ulcer at the site of the tick bite was still present, but it was smaller and less painful (Fig. 3). Laboratory results showed improvement, and the C-reactive protein and sedimentation rate were declining.

Discussion

Tularemia, or rabbit fever, is a zoonotic bacterial infection caused by the bacterium F. tularensis, a Gram-negative coccobacillus. Most infections in humans are caused by F. tularensis subsp. holarctica and tularensis. The less contagious F. tularensis subsp. holarctica is widespread in Europe (1–3).

In 2019 the ECDC reported 1,463 confirmed cases of tularemia in Europe, most of them in northern Europe. The incident rate was 0.3 cases per 100,000 population (7). In 2021, a major outbreak of tularemia was recorded in the Gorizia region in Slovenia, and in July alone 27 cases were confirmed. The cause was contaminated water in three private water mains (4, 5).

In nature the main reservoirs are mammals. Humans become infected through arthropod bites, direct contact with an infected animal, ingestion of contaminated water or food, and inhalation of contaminated aerosol (1, 2, 8). The incubation period is usually short, 3 to 5 days, but it can last up to 21 days. The clinical manifestations of tularemia depend on the route of inoculation, and they range from cutaneous ulcers to pneumonia (1, 2, 8, 9). Tularemia should be suspected in patients with compatible clinical symptoms and epidemiological risk factors.

The first patient had oropharyngeal tularemia, a very rare form of the disease. It emanated from an oropharyngeal portal of infection, most likely through ingested contaminated food or water. An examination showed unilateral exudative pharyngitis, tonsillitis, and cervical supplicative lymph node enlargement. Ultrasound is the diagnostic test of choice for assessing the type of lymphadenitis; our patient had a conglomerate of lymph nodes 7 to 17 cm in size shown on the sonography. Suppuration of affected lymph nodes is a relatively common complication and may occur despite antibiotic therapy, which also occurred in our patient, who was treated with doxycycline. Oropharyngeal tularemia should be suspected in patients with unilateral tonsillopharyngitis and...
lymphadenitis when conventional antibiotic therapy with beta-lactam antibiotics has failed (1–3, 10, 11).

The second patient had ulceroglandular tularemia, which is the most common form of the disease (> 80 %). As the name suggests, it is characterized by enlarged lymph nodes and an ulcer on the skin. At the site of the infected tick bite, a painful papule first develops, which turns into a painful ulcer with a raised edge. Lymphadenopathy may occur before the ulcer, at the same time, or slightly later (1–3). The patient had a fever and a single erythematous papulo-ulcerative lesion with a central eschar at the site of a tick bite. The axillary lymph nodes were not palpable, but the axillary area was painful. Treatment with beta-lactam antibiotics was ineffective, and even after treatment with doxycycline the condition improved only partly. The ulcer gradually decreased and healed with scarring.

Both patients had non-specific symptoms such as fever, chills, muscle, or abdominal pain and fatigue, which are common to all forms of tularemia (1, 2, 12).

Black eschar is also characteristic for rickettsial infections; we did not include it in our set of diagnostic tests because the patient denied recent travel and we had an outbreak of tularemia at that time.

Tularemia was confirmed in both cases by serological testing. In the second case, the serological tests were initially negative, and IgG and IgM antibodies for *F. tularensis* were detected 4 weeks after the onset of symptoms. Infection with *F. tularensis* is primarily diagnosed based on serological methods (ELISA, agglutination test, and indirect immunofluorescence assay). It takes at least 2 to 3 weeks after infection for antibodies to be detectable, and the diagnostic rises in convalescent antibody titers appear 4 to 6 weeks after the onset of symptoms. A positive agglutination test is considered a titer > 1:160 or a four-fold increase in the convalescent phase. A negative serological test does not rule out infection, and therefore it is advisable to repeat the test in 2 to 4 weeks. In the second case, we showed the importance of repeated serology (1, 2, 13).

The sensitivity of serology increases with the duration of the disease. As shown previously, the ELISA method performed better for early detection of specific antibodies; however, ELISA also had more false-positive results (13). A false-positive result can occur due to cross-reactions with *Brucella* spp. and less commonly with *Yersinia* or *Salmonella* spp. Positive serology may persist for years after infection (titer 1:20–1:80) (1, 2, 13). The bacterium was also confirmed by PCR on a cervical lymph node smear (the first patient) and from skin biopsy from the ulcer area (the second patient). PCR of the affected lymph nodes in cases of glandular or oropharyngeal tularemia may be an effective diagnostic technique. In some studies, PCR was positive in the lymph node aspirates, even though the patients had been receiving antibiotics for more than 2 weeks. False-negative results can occur in the presence of inhibitors in the clinical sample, such as heme in whole blood samples (14). In our second patient, the first PCR was negative; the possible cause could be a poorly taken swab sample. This example shows the importance of repeating testing if there is a strong clinical suspicion.

A histopathological evaluation should follow as a diagnostic in persistent lymph node and skin ulcer pathologies; however, in our case, this was not performed (1, 2, 10). Secondary cutaneous manifestations are thought to be common in tularemia (estimated at 50%) but are often overlooked or misdiagnosed. Maculopapular or vesiculopapular rashes, erythema multiforme, erythema nodosum, and urticaria have been reported in the literature. Erythema nodosum was seen more often in patients with pulmonary tularemia (3, 15).

Tularemia may be a self-limiting disease, but antibiotic therapy can prevent complications, shorten the duration of the disease, and reduces mortality. The dosing and duration of treatment with antimicrobial agents are not well defined. Usually it is treated with aminoglycosides (gentamicin or streptomycin), tetracyclines, and fluoroquinolones (1, 2, 16, 17). The duration of treatment depends on the antibiotic. Aminoglycosides require intravenous administration but are generally considered the more effective agents. Tetracyclines are bacteriostatic, and so treatment must be administered for a minimum of 2 weeks, and higher relapse rates have been reported compared to fluoroquinolones (16, 17).

The literature describes cases of antibiotic therapy failure and relapses, which are often associated with delayed and/or insufficiently long treatment. Suppurated lymph nodes often need to be removed surgically to obtain a clinical cure (17, 18).

Due to the COVID-19 epidemic, there was no infectious disease ward at our hospital, and so both patients were treated as outpatients. In our patient with oropharyngeal tularemia, therapy with doxycycline was only partially effective, and so antibiotic therapy was switched to ciprofloxacin. After ciprofloxacin therapy, the purulent secretion stopped, the lymph node gradually shrunk, and a small scar formed at the site of the fistula.

In cases of confirmed contact with tularemia, post-exposure prophylaxis with ciprofloxacin 500 mg bid or doxycycline 100 mg bid for 14 days is recommended. Some live vaccines are still being developed (19, 20).

**Conclusions**

Tularemia is an uncommon disease; only some individual cases are recorded each year in Slovenia. The clinical picture is very broad and varies depending on the route of inoculation. Common to all forms are non-specific symptoms, such as fever, chills, muscle or abdominal pain, diarrhea, and headache, and so the differential diagnosis is very diverse. The diagnosis of tularemia is often delayed for these reasons. Tularemia should be considered in ulcerative skin lesions and associated lymphadenitis following a previous tick bite or in people that handle rabbits, and in cases where antibiotic therapy with beta-lactam antibiotics is ineffective. In most cases it is a self-limiting disease, but antibiotic therapy can prevent complications, shorten the duration of the disease, and reduce mortality, especially in the case of pulmonary tularemia.

**References**


