

Two cases of tick-borne transmitted tularemia on Southern Zealand, Denmark

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Case report

Title: Two cases of tick-born transmitted tularemia on Southern Zealand, Denmark.

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Running head: Two cases of tick-born transmitted tularemia on Southern Zealand, Denmark.

Summary

Francisella tularensis is a zoonotic bacterium that causes the infection tularemia. It colonises invertebrates and vertebrates, counting wildlife animals and rodents. Humans can become infected through several pathways including contaminated food, water, handling animals and due to bites from vectors. Ticks are known to cause tularemia in humans, though their role as a disease transferring vector is not well understood. We describe two case reports of tularemia transferred by ticks on Southern Zealand, Denmark.

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Case 1: A 49-year-old woman presented with lymphadenopathy and an unhealed sifting wound after a tick bite. Serology tests for *F. tularensis* were initially negative but turned positive five weeks after symptom onset, when abscess drainage was performed. Gentamycin and ciprofloxacin treatment improved the patient's clinical condition, and she completely recovered.

Case 2: A 74-year old man presented with malaise, fever and an abdominal ulcer allegedly caused after a vector bite. CRP and leukocytes were increased, while serology tests for *F. tularensis* were negative. Doxycycline treatment improved the patient's clinical condition, and he completely recovered. Three weeks after symptom onset renewed serology tests for *F. tularensis* were positive.

Keywords: Francisella tularensis, Tularemia, zoonotic disease, lymphadenitis, bacterial infection, tick borne.

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Introduction

We describe two cases of confirmed tularemia transferred by ticks on Southern Zealand, Denmark. The bacterium is a pleomorphic, gram-negative coccoid rod that grows strictly aerobic on enriched media supplemented with cysteine and cystine. It is non-motile and slow growing (2-4 days) with transparent, mucoid and easily emulsified colonies. The bacterium is weakly catalase-positive and oxidase-negative.^{1,2} The pathogen can be transmitted to humans through contact with infected animals, contaminated aerosols, food and water as well as bites from vectors.³ Among others, rodents, hares and rabbits constitute a reservoir for the bacteria. The relevance of ticks and mosquitos as vectors and reservoir remains to be elucidated.⁴ Currently four subspecies of *F. tularensis* have been identified: *novicida*, *tularensis*, *mediaasiatica* and *holarctica*.² The only known occurring subspecies in Denmark is *F. tularensis* subsp. *holarctica*, which is prevalent in Asia and Europe, whereas *F. tularensis* subsp. *tularensis* is predominant in Northern America.² *F. tularensis* subsp. *holarctica* is less virulent than subsp. *tularensis* and is not susceptible to commonly used antibiotics such as penicillin and cephalosporin, while one specific subtype shows

resistance to erythromycin.^{5,6} Only few data are available concerning the susceptibility of clindamycin, with one study reporting resistance to all tested strains.⁷

Up to six different clinical manifestations by infection with *F. tularensis* have been distinguished and are classified by the infectious portal of entry.¹ We describe two cases of glandular tularemia, a condition generally characterised by a sudden onset of flu-like symptoms including chills, fever, headache and prostration. The infection spreads lymphatically and typically develop regional suppurative lymphadenopathy, which may further progress into sepsis with risk of fatal outcome.¹ The glandular form is known to have considerable period of convalescence, and untreated disease may cause protracted symptoms.² Treatment involves gentamicin, ciprofloxacin or doxycycline.^{1,8,9} Tularemia is considered a sporadically occurring disease in Denmark, with approximately four cases per year. It might be underdiagnosed to a certain degree due to prolonged symptoms and unclear aetiology.⁶

Case 1

A 49-year-old woman was bitten by a tick on her right foot in relation to an outdoor picnic early June 2016. She discovered the tick and removed it on the following day. During the next couple of days, she developed fever progressing to temperatures of 39.5°C followed by malaise and enlarged lymph nodes in the right inguinal region. She consulted her general practitioner and was given penicillin on suspected borrelia infection, though no erythema migrans rash was apparent. Two weeks after initial symptoms she was admitted to a Danish hospital. Examination revealed a tiny unhealed wound between second and third toe on her right foot with flushing and sifting of clear fluids. She had a heavily enlarged lymph node in her right inguinal region measuring 8x3 cm with local flushing and soreness. Her fever had subsided, and she had moderately increased CRP of 65 mg/L (reference range less than 10 mg/L) and leukocytes of $8.4 \times 10^9/L$ (reference range $4.5-11 \times 10^9/L$). Ultrasound of the right inguinal region revealed inflammation of the lymph nodes and the hypodermis with no sign of abscess formation. Doxycycline treatment 100 mg twice daily was initiated on clinical suspicion of tularemia, and penicillin treatment was stopped. She was then discharged home with planned follow-up as an outpatient. Pus from the unhealed wound on her toe was tested by PCR and found positive for *F. tularensis* DNA.¹⁰ Serological tests for *F. tularensis* as well as for other tick-borne bacteria (Borrelia, Anaplasma, Bartonella, Rickettsia) were negative.

The patient met three weeks later for planned follow-up and was hospitalised in the department of infectious diseases due continued enlargement of the lymph node in the inguinal region. The lymph node was fluctuant, flushing and soreness had increased, and ultrasound revealed abscess formation. The patient had general symptoms, CRP had decreased to 37mg/L and leukocytes were $9.8 \times 10^9/L$. Renewed serological tests for *F. tularensis* antibodies were positive with high titers of 200 (cut-off value <25). The abscess was incised and drained for 8 mL pus, which was submitted for PCR test and culturing. *F. tularensis* DNA was present, but the bacteria were not recovered by culture. Doxycycline treatment was stopped, and she was given a 21-day course of ciprofloxacin 750 mg twice daily as well as a single dose gentamycin of 400 mg. A week later, *F. tularensis* antibodies were measured to titers of 400. During the next few months the abscess wound had continued sifting of fluids but gradually healed. The patient experienced fatigue but slowly recovered completely during the next 6 months.

Case 2

A 74-year old man presented to a Danish hospital in July 2018 with a few days of general symptoms and rapidly increasing fever measuring 41.1°C. He had complaints of headache, dizziness, lumbar pain, pharyngitis and diarrhea. In addition, he had a minor itchy ulcer on the abdomen with surrounding dusky erythema that did not appear to be infected. It had been present a few days prior to symptom onset and though no insect or tick had been observed, the patient expected it to be due to a bite since he went for daily forest walks. Blood samples showed moderately elevated CRP of 89 mg/L and leukocytes of $9.8 \times 10^9/L$. The patient was then given intravenous piperacillin and tazobactam.

During the next couple of days, the patient had persistent fever and increasing infection rates with CRP up to 182 mg/L and leukocytes of $10.4 \times 10^9/L$. Dermatological assessment of the stomach ulcer deemed an eschar and was a priori suspected to be African tick bite fever. However, as the patient had not traveled out of Denmark for 10 years the most likely diagnosis was tularemia. Though serological tests for *F. tularensis* and other tick-borne bacteria were negative, treatment was changed to doxycycline 100 mg twice daily on clinical suspicion of tularemia. A few days after doxycycline treatment was initiated, the patient improved clinically and was discharged for continued treatment for a total of three weeks. Renewed serological tests for *F. tularensis*

antibodies were positive with antibody titers of 400, three weeks after symptom onset. After five weeks the patient suffered from fatigue but otherwise slowly recovered completely.

Discussion

Here we describe two case reports of tick-transferred tularemia detected on Southern Zealand, Denmark, in which both cases were of glandular type. Both patients were initially diagnosed on the basis of clinical suspicion before serological tests turned positive. In case 1, serological tests for *F. tularensis* were negative after 14 days and turned positive 5 weeks after symptom onset. In case 2, serological tests were negative after 7 days and turned positive 3 weeks after symptom onset. Serological tests for *F. tularensis* are known to remain negative for at least ten days after exposure and may take several weeks to become positive, which was also the case here.¹ In case 1, sampled pus from the toe wound was tested by PCR and turned positive with *F. tularensis* DNA after two weeks. Presence of bacterial DNA from either pus or aspirates from lymph nodes can be tested early during *F. tularensis* infection and is a sensitive method. However, serological tests are still needed to confirm ongoing infection.¹¹

The patient in case 1 had received three weeks of treatment with doxycycline and still had increased CRP. The treatment did not eradicate *F. tularensis*. Prior to doxycycline treatment the patient was treated with penicillin on the basis of suspected borrelia. While penicillin is ineffective in the treatment of tularemia, doxycycline is a recommended drug according to guidelines.⁸ In case 2, treatment with doxycycline decreased the CRP and leukocytes and improved the overall clinical condition of the patient. Treatment of *F. tularensis* subsp. *holarctica* with doxycycline is associated with a higher rate of failures and relapses as well as prolonged disease course compared to treatment with aminoglycosides and fluorquinolones.¹² This may explain the lack of effect in case 1.

Most cases of tularemia in Denmark are generally believed to be caused by either physical contact with infected animals (especially game) or tick bites.¹³ Four case reports of tick transmitted *F. tularensis* have been reported in Denmark in 2014, including two cases on Northern Zealand.¹⁴ However, no documentation of tick bites was evident in the described cases. We are convinced that tick bites were responsible for the development of tularemia in the cases described here. It is however a limitation that we have not been able to inspect and test the suspected disease

transferring ticks for *F. tularensis* to support our theory. Our knowledge of ticks as the disease transferring vectors in this case report is therefore solely based on anamnestic information. The patient in case 1 allegedly observed and removed a tick in relation to the occurring disease. The patient in case 2 did not observe any tick but the history was highly suspicious for a tick bite. As an alternative way of transmission, it could be considered whether a mosquito could transfer the disease. Mosquitoes are known to play a dominant role as vectors in transferring tularemia in Finland and Sweden, yet not confirmed in Denmark.^{15,16}

These cases strengthen the idea of ticks being an important but unrecognised vector for the transmission of tularemia to humans. This is an area of future interest, since the role of ticks and insects as vectors for *F. tularensis* is generally not well understood.

Conflict of interest

The authors have no conflicts of interest or any financial disclosures to report.

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Ethical statement

No human or animal subjects were used for making this case report. Written consent was obtained from the patients for using the medical histories and photographs.

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Images:



Fig. 1. Case 1: Healed wound after tick bite on right foot 5 weeks after exposure.

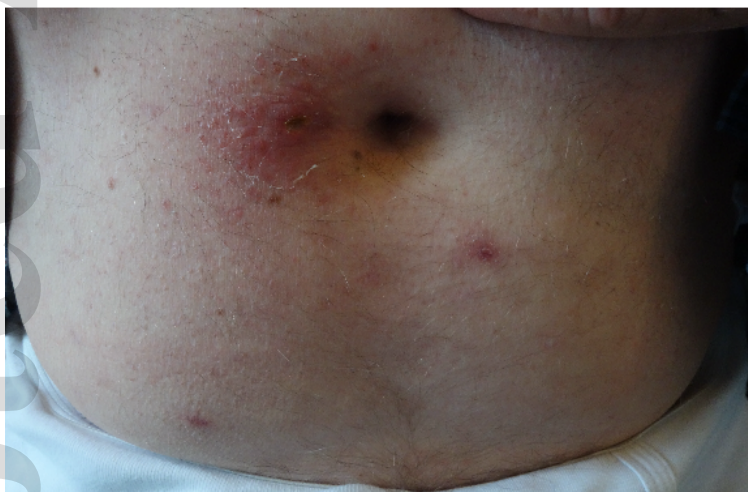


Fig. 2. Case 2: Abdominal ulcer a few days after suspected tick bite