



Case report

The clinical spectrum of tularemia—Two cases

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ABSTRACT

We report two cases of tularemia with different clinical manifestations, both suspected of tick-borne transmission and with near-complete remission of all symptoms within 3 months after antimicrobial treatment. The first patient presented with a classical ulceroglandular manifestation; general malaise, an ulcer and lymphadenopathy, occurring two weeks after a tick bite. Diagnosis was established by polymerase chain reaction of a skin biopsy from the ulcer. The second patient presented with a rare systemic manifestation including bacteremia and myocarditis resulting in severe clinical heart failure, pulmonary edema and secondary kidney failure. Previous tick bites were elucidated after the bacteremia was discovered. The cases underscore the heterogeneity of manifestations, the diagnostic approach and the importance of thorough medical history including recent exposures especially in cases with infection of unknown origin.

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Introduction

Tularemia also called rabbit fever is a zoonotic disease endemic to the Northern hemisphere and caused by the highly infectious gram-negative bacterium *Francisella tularensis* [1,2]. Two subspecies are known to be the main causes of human disease; *F. tularensis holartica*, is prominent in Europe and less virulent than *F. tularensis tularensis* which is mainly found in North America [1,3]. Transmission is commonly mediated through arthropod bites, by direct contact with infected animals, ingestion of contaminated water or meat or by inhalation or conjunctival exposure of aerosols [2,4,5]. Early clinical presentation usually includes flu-like symptoms such as fever, myalgia, arthralgia and headache, but further symptoms depend on bacterial virulence, host immune status and on the route of transmission. The inoculation site will often show signs of localized infection with an ulcer and/or lymphadenopathy. Pharyngitis, pneumonia and painful conjunctivitis are normally related to the other routes of transmission. Hematogenous spreading and complications such as systemic disease, pneumonia, formation of abscesses and lymph node suppurations can be seen in relation to all forms of infection. Thus, tularemia can be a prolonged and debilitating disease especially in cases of delayed treatment [2,4].

Tularemia is widespread across Europe with highest incidences in Sweden and Finland but only sporadic occurring in Denmark and in risk of being overlooked or misdiagnosed [3,4]. In this present article, we describe 2 cases with different clinical manifestation due to tularemia, by this we aim to bring light on a possible underdiagnosed disease.

Case 1

A 63-year-old female was hospitalized in April 2019 presenting with general malaise and a non-healing ulcer on her right ankle with adjacent lymphadenopathy following a tick bite two weeks prior to admission. The patient had previously been diagnosed with hepatic steatosis without indication for medical treatment. The day after tracking badgers on a wood hike 15 km west of Copenhagen, the patient discovered a tick on her right ankle. The tick was removed and 24 h later signs of infection and discomfort began. Over the next two weeks fever (38–39 °C), chills, myalgia and right-sided inguinal glandular swelling developed. At admission, her laboratory testing showed increased hepatic and infectious parameters (Table 1). Doxycycline 100 mg twice daily was initiated upon clinical suspicion of rickettsial disease. A skin biopsy and blood serology were obtained, and tularemia was investigated as a differential diagnosis. Serological tests investigating *rickettsiae* and *F. tularensis* were negative. The diagnosis was established with a positive Polymerase Chain Reaction (PCR) for *F. tularensis* DNA from the ulcer biopsy. Doxycycline was administered for 10 days with immediate effect on wound healing. The first

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Table 1
Comparison of clinical and paraclinical characteristics.

	Case 1	Case 2		
Sex	Female	Female		
Age	63 years	76 years		
Exposures	Tracking badgers on wood hike	Vacation home in high risk area		
Previous tick bite	Yes	Yes		
Duration of symptoms (from onset to admission)	14 days	21 days		
History with fever	Yes	Yes		
Clinical manifestation	Local infection	Systemic infection		
Symptoms at admission	Ulcer, lymphadenopathy and general malaise.	Myocarditis with clinical heart failure, pulmonary edema and secondary kidney failure		
Laboratory test	Admission	Admission	Readmission	
	Reference levels			
WBC	3,500–8,800 cells/ μ L	11,000 cells/ μ L	24,000 cells/ μ L	17,000 cells/ μ L
CRP	0–10 mg/L	97 mg/L	271 mg/L	27 mg/L
Platelets	145,000–390,000 cells/ μ L	–	461,000 cells/ μ L	767,000 cells/ μ L
ALT	10–45 U/L	136 U/L	–	–
LDH	105–205 U/L	237 U/L	–	–
ALP	35–105 U/L	191 U/L	–	–
Creatinine	50–90 μ mol/L	–	–	179 μ mol/L
Potassium	3.5–4.4 mmol/L	–	–	5.4 mmol/L
Tnl	25–45 ng/L	–	3,520 ng/L	–
CPK	< 4 μ g/L	–	20 μ g/L	–
Diagnostic approach	Positive PCR from skin biopsy Specific <i>F.tularensis</i> IgG and IgM negative	Positive blood cultures Specific <i>F.tularensis</i> IgG and IgM status unknown		
Antimicrobial treatment	10 days doxycycline	6 days piperacillin/ tazobactam 4 days amoxicillin/clavulanic acid 21 days doxycycline		
Mode of transmission	Tick-borne	Tick-borne		
Outcome	Complete remission and wound healing were seen within 3 months.	Near-complete remission within 3 months including withdrawal of most cardiac medicine.		

Abbreviations: ALT, alanine transaminase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; WBC, white blood cells count; CRP, C-reactive protein; Troponin I, Tnl; creatine phosphokinase, CPK.

months after treatment was dominated by fatigue and muscle pain. Complete remission and wound healing were seen within two months and hepatic parameters normalized after approximately 3 months.

Case 2

A 76-year-old female with a high daily functioning presented with clinical heart failure, pulmonary edema and fever in July 2019. In the weeks prior to admission she had suffered from fever, chills and fatigue including progressive respiratory difficulties. Her symptoms had initially been ascribed as influenza by her primary physician without initiation of treatment. At admission her thoracic X-rays showed severe pulmonary stasis and echocardiogram established a biventricular failure with an ejection fraction (EF) of 10 %. Laboratory testing showed elevated troponins and increased infectious parameters (Table 1). Coronary arteriography was without significant stenosis excluding relevant coronary heart disease. Based on a ventriculography Takotsubo's cardiomyopathy was hypothesized as the primary cause of her cardiac failure and she was treated symptomatically with diuretics, antihypertensive and antiarrhythmics. As she continued to be feverish piperacillin/tazobactam was administered for a total of 6 days. Over the following week her condition improved considerably with increasing EF (40 %) and decreasing CRP (81 mg/L). She was discharged with planned 8 days treatment of amoxicillin/clavulanic acid.

Three days later blood cultures tested positive for *F. tularensis*. Directly asked, the patient recalled multiple tick-bites, during her stay in West Zealand with the latest being in the beginning of June 1–2 weeks prior to onset of symptoms. She did however not recollect any prior skin infection or lymphadenopathy. At readmission she was well and without respiratory symptoms.

Her laboratory tests revealed decreasing infectious parameters and signs of kidney failure (Table 1). Antimicrobial treatment was changed to doxycycline orally for a total 21 days and all nephrotoxic treatment were terminated. The first month was dominated by fatigue and shortness of breath and slightly increased WBC. She was followed in an out-patient clinic with near-complete remission of all parameters within 3 months including withdrawal of most cardiac medicine.

A comparison of the clinical presentation of the cases is presented in Table 1.

Discussion

Due to environmental and climatic changes the geographical distribution of vector-borne infections is changing and incidences increasing [6]. *F. tularensis* has been detected in increasingly new settings and in a wide range of wild species [1–3] and more cases have recently been reported from Sweden and a few cases from Denmark [1,7,8].

In both cases, tularemia was not the suspected diagnose at admission. A tick-borne disease was suspected in the first case and relevant diagnostics tests and antimicrobial therapy initiated. However, in the second case the patient's exposure to ticks prior to the onset of symptom was first realized after the diagnosis was established. These findings underscore the importance of anamnestic information of exposures and that patients with relevant exposure and infection of unknown etiology should be investigated for a tick-borne infection including rare infections such as tularemia. Diagnostics combines clinical manifestation with the detection of *F. tularensis* either by serology, cultures or DNA [2]. However, specific antibodies are only detectable after weeks of infection as was the case in the first patient. PCR has been demonstrated to be more sensitive than cell culture in skin ulcers

and lymph nodes suppurations [4]. *F. tularensis* is highly infectious and cultures should be handled under appropriate biosafety conditions in order to avoid laboratory infection [9,10].

The heterogeneity of symptoms in tularemia is largely explained by mode of transmission [4,5]. But where the first case manifested with classic tick-mediated symptoms (i.e. skin and lymph node involvement) [4], the second case displayed systemic symptoms without skin infection. *F. tularensis* can spread hematogenous and systemic disease can be a complication to all forms of tularemia, however pneumonia is typically related to the inhalation of aerosols [2,9] and as the patient had a vacation home in a high-risk area, she could have inhaled aerosols for example in connection to lawn moving [5]. Myocarditis has been reported as a complication to tularemia in at least one other case with tick bite as point of entry [5].

Fluoroquinolones, tetracyclines and aminoglycoside are all effective therapy for *F. tularensis* with cure rates varying between 60–100% [11], because of the toxicity of aminoglycosides and the need for intravenous administration, tetracyclines and fluoroquinolones are first-line drugs for treatment of mild to moderate tularemia and should be given for 14–21 days depending on clinical status [4,12]. Some studies have reported tetracyclines to have higher rates of relapse compared to fluoroquinolones [7,11]. Our patients both reported marked improvement of symptoms following antimicrobial treatment and no relapse or subsequent complications were seen, but they also reported to be suffering from fatigue, myalgia or shortness of breath the following 2–3 months. The first patient only received 10 days of treatment, but since she initiated treatment early and responded without signs of complications, it was decided to be sufficient. The second case was initially treated with piperacillin/tazobactam. *F. tularensis* is usually not susceptible to beta-lactams [9]. She initially had a partial clinical and paraclinical improvement, but later her infection continued to progress, and she developed secondary kidney failure. After initiation of treatment with doxycycline she improved, and her kidney function normalized after 4 weeks. Late diagnosis is correlated with a more severe course of tularemia, and an increased risk of long-term sequelae [11]. It is therefore important to be aware of tularemia as a differential diagnosis to otherwise unexplained infections particularly in cases with high exposure to animal wildlife, ticks and mosquitoes.

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Consent

Written informed consent was obtained from the patients for publication of this case report.

Author contribution

All authors contributed substantially to the design of the study and to the acquisition of data. MO drafted the manuscript, MH and

AML critically revised, commented on and approved the final manuscript.

CRedit authorship contribution statement

Mathilde Ørbæk: Conceptualization, Investigation, Writing - original draft. **Anne-Mette Lebech:** Conceptualization, Investigation, Supervision, Writing - review & editing. **Marie Helleberg:** Conceptualization, Investigation, Supervision, Writing - review & editing.

Declaration of Competing Interest

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