Case Report
Long-Lasting Fever and Lymphadenitis: Think about F. tularensis

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We report the case of glandular tularemia that developed in a man supposedly infected by a tick bite in Western Switzerland. Francisella tularensis (F. tularensis) was identified. In Europe tularemia most commonly manifests itself as ulcero-glandular or glandular disease; the diagnosis of tularemia may be delayed in glandular form where skin or mucous lesion is absent, particularly in areas which are assumed to have a low incidence of the disease.

1. Clinical History

A 75-year-old man, living in a rural area of Western Switzerland, was admitted to the regional hospital in mid-July 2013 presenting with fever and myalgia lasting for 5 days. Family members reported periods of confusion over the previous 24 hours. He never traveled abroad. He is retired from the postal service and spent his free time walking in the forest. He had no direct contact with domestic or wild animals. Medical history revealed diabetes type II and hypertension.

On admission the patient was febrile with moderate agitation and confusion. There was no neck stiffness and the neurological exam was unremarkable. Except for a painless partially encrusted lesion on the left leg, the clinical exam was assessed as normal. A brain computer tomography (CT) and magnetic resonance imaging (MRI) excluded pathological finding. Cerebral spinal fluid (CSF) analysis displayed $5.2 \times 10^6$ mononuclear cells (reference value $<3.0 \times 10^6/L$) and normal levels of protein and glucose. Blood test showed a mild elevation of CRP at 23 mg/L (reference value $<5$ mg/L).

The screening for the most common infectious causes of encephalitis was performed including serological testing of human immunodeficiency virus (HIV), immunoblot for Lyme disease in serum and CSF, and molecular tests for Herpes simplex virus (HSV), Varicella-zoster virus (VZV), Listeria monocytogenes, and Bartonella henselae (B. henselae) in CSF. All were negative. CSF and blood cultures were negative.

Patient was treated with ceftriaxone and acyclovir for 48 hours. He spontaneously recovered and was discharged home after 5 days but was readmitted a few days later with relapsing fever, confusion, and extreme fatigue. Clinical exam was unchanged. Radiological workup including chest and abdominal CT performed for investigation of fever of unknown origin (FUO) revealed enlarged left femoral lymph nodes. Because of the presumption of lymphoma, lymph node biopsy was ordered. Histological examination revealed a lymphadenitis with follicular hyperplasia including immature B lymphocytes on immunohistochemistry (IHC) and sites of necrosis containing numerous granulocytes surrounded by epithelioid cells (Figures 1(a) and 1(b)). There was no sign for oncologic or infectious process. Bacteria, including B. henselae and mycobacteria, were not detected by Gram, Warthin-Starkey, and Ziehl-Neelsen stains. Serology for Epstein-Barr virus (EBV) showed past infection. Serology for B. henselae (IgG titer 1000, N < 120; IgM titer < 100, N < 100) was compatible with a current or an ancient infection.
Figure 1: (a) HE, 4x: lymphadenitis with follicular hyperplasia and necrosis (arrow) surrounded by a histiocytic reaction. (b) HE, 20x: necrotizing and granulomatous lymphadenitis, with numerous neutrophils (arrow).

However, *B. henselae* specific PCR performed on paraffin-embedded lymph node, as described below, was negative.

Serology for *F. tularensis*, performed by enzyme-linked immunosorbent assay (ELISA) one month after the onset of clinical manifestation, was compatible with a recent infection (IgG 300 U/mL, N < 10; IgM 122.4 U/mL, N < 10). Definite diagnostic of tularemia was confirmed by detection of *F. tularensis* DNA (600 copies/mL) extracted from formalin-fixed and paraffin-embedded tissue sections of the femoral lymph nodes, as described below. Briefly, several tissue sections were obtained from the pathologists and collected in sterile tubes. After removal of paraffin using Xylol (65°C) and further rehydration via decreasing concentrations of ethanol washes, DNA was extracted using MagNA Pure LC automated system (Roche) with the MagNA Pure LC DNA isolation kit I (Roche) and eluted in a final volume of 100 μL. Francisella specific PCR, targeting the *fopA* gene as previously reported [1] and *B. henselae* specific PCR targeting the *htr A* gene were performed.

The patient recovered after completion of 3 weeks of ciprofloxacin treatment.

### 2. Discussion

Tularemia is a zoonosis mainly occurring in the Northern Hemisphere. Humans may acquire the disease through the handling of infected animals, ingestion of contaminated food or water, inhalation of infective aerosols, and hematophagous arthropod bites [2]. *F. tularensis*, the agent of tularemia, comprise 3 subspecies: *F. tularensis* subspecies (subsp.) holarctica, *tularensis*, and mediastatica. *F. tularensis* subsp. *tularensis* and *F. tularensis* subsp. *holarctica* are clinically relevant for humans. *F. tularensis* subsp. *tularensis* is only present in North America, while the subspecies *holarctica* is widespread in the whole Northern Hemisphere [3]. Infection with *F. tularensis* leads to 6 major clinical manifestations primarily reflecting the route of infection and comprising ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, and typhoidal syndrome. However, tularemia may present with nonspecific symptoms and routine laboratory testing, hampering its rapid diagnosis, especially in new endemic region. Ordinarily the onset of disease is abrupt occurring in an average of 3 days but ranging from 3 to 30 days after exposure. Fever, chills, and headache malaise are frequent. Persistent high fever is common. Ulceroglandular form is the most common form in Europe, presenting commonly as a localized lymphadenopathy. The initial skin lesion appears as a cutaneous ulcer, usually solitary and evolving over the course of the disease in “encrusted,” “ulcerous,” or “pustular” wound [4].

The histologic examination of the regional lymph node revealed a necrotizing and granulomatous lymphadenitis [5]. Granulomatous lymphadenitis may be representative of infectious or noninfectious processes. Noninfectious causes encompass sarcoidosis or sarcoid-like reaction observed in many underlying diseases. Infectious lymphadenitis is histologically categorized into suppurative or nonsuppurative, according to the presence or absence of granulocytes in necrotic area. Follicular hyperplasia, B lymphocytosis, histiocytic reaction, and granuloma with numerous granulocytes in central necrosis are characteristically depicted in adenitis associated with *F. tularensis* and *B. henselae* infection [6]. In opposite, nonsuppurative adenitis, characterized by granulocyte-free necrosis, is described in *Mycobacterium tuberculosis* and *Toxoplasma gondii* infections. Thus, in absence of available tissue for culture, histological description may presume the involved microorganism and suggest additional tests to establish a definite diagnosis. Tularemia is generally diagnosed either by serological tests comprising microagglutination and enzyme-linked immunosorbent assays (ELISA), by isolation of *F. tularensis*, or by performing a specific *F. tularensis* PCR from clinical material including wound drainage, lymph node aspirate, sputum, and blood. The isolation of the agent of tularemia by culture or the detection of *F. tularensis* DNA by PCR on fresh and frozen tissues is particularly useful in the early phase of the disease when antibodies are not yet present and the treatment is more effective [7].

In the present case the diagnosis was evoked lately in spite of suggestive clinical and histological clues including febrile lymphadenitis, encrusted cutaneous lesion attributed to arthropod bite, and suppurative granulomatous adenitis. While arthropod-borne diseases such as tick-borne encephalitis and Lyme disease are well known by physicians,
tularemia is still rarely evoked by doctors in Switzerland, despite an increasing number of reported cases since 2008 [8–11]. A study published in 2000 reported that out of 6071 Ixodes ricinus ticks collected on Swiss Army training grounds in five regions of Switzerland, 0.12% harbored F. tularensis DNA [12].

Nervous system abnormalities are uncommon manifestations of tularemia and have been exceptionally reported as meningitis and encephalitis, probably following meninges seeding during untreated bacteremia [13–16]. Meningitis or encephalitis may occur following all of the 6 syndromes caused by F. tularensis, developing in a median of 5 days, ranging from 3 to 30 days after the onset of initial manifestation [17]. CSF analysis usually reveals mononuclear pleocytosis, variable level of protein and glucose, and generally negative Gram stain [17, 18]. Based on unremarkable CSF analysis and CNS radiologic evaluation, the cause of the confusion and the contribution of F. tularensis in the abnormal behavior observed in our patient could not be established.

Aminoglycosides (streptomycin and gentamicin), fluoroquinolone, and tetracyclines are the drugs commonly used to treat tularemia. Until recently macrolides were considered effective in cases acquired in Switzerland and Western European countries. Azithromycin was even considered as effective in cases acquired in Switzerland and Q fever. Because of its IV formulation and side effects, its use is currently restricted to severe tularemia cases. Fluoroquinolone may be considered as the first line treatment in lowest MIC compared to that of other effective antibiotics, quinolone may be considered as the first line treatment in severe tularemia.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References


