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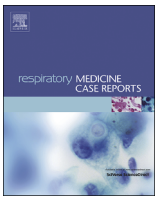

Case Report

Francisella tularensis subsp. *holarctica* bacteraemia in an immunocompetent male

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ABSTRACT

Tularemia is a rare zoonotic disease caused by the two predominant subspecies of Francisella tularensis, namely subspecies tularensis and subspecies holarctica. The latter is less virulent than the former, is endemic in Europe, and usually has a mild disease course, although respiratory involvement and bacteraemia can occur. Tularemia in Belgium is rare, but the incidence seems to be increasing. It therefore seems prudent to raise awareness among clinicians for this potentially severe disease. We report the first case of pneumonic tularemia with bacteraemia from Belgium, and want to recommend including Francisella tularensis in the differential diagnosis of pneumonia when an unfavorable evolution is seen with standard treatment.

1. Introduction

Tularemia is a rare zoonotic infection, caused by the gram-negative coccobacillus *Francisella tularensis*. This highly virulent microorganism resides predominantly in the northern hemisphere and the main animal reservoir consists of lagomorphs (e.g. hares and rabbits) and rodents (e.g. mice, rats, squirrels,..). The bacterium can also survive outside of an animal host (i.e. surface water, dust, dew) [1]. Transmission from animals to humans occurs via arthropod vectors (ticks, mosquitos) or via direct contact (inhalation, inoculation, ingestion of infected wild animals). The average incubation period is 3–5 days, but both shorter (from 1 day) and longer (up to 20 days) periods have been described. Symptoms can be non-specific, certainly in the early stage of the disease, but common symptoms include fever and lymphadenopathies. The clinical presentation of the disease varies depending on the route of transmission, thus distinguishing an (ulcero)glandular, oculoglandular, oropharyngeal, pulmonary or typhoidal form. Combinations of these forms have also been described [2].

The most common clinical syndrome worldwide is (ulcero)glandular tularemia, when transmission occurs by a vector or direct animal contact, and is characterized by regional lymphadenopathy with or without a typical skin ulcer [2,3]. Pulmonary tularemia can be caused by inhalation, but also through hematogenous spread from another disease presentation. Typhoidal tularemia refers to a systemic form of the disease with no clear route of transmission.

Today, four subspecies of *Francisella tularensis* are known, which differ in virulence, geographical distribution and disease presentation. *Francisella tularensis* subspecies *tularensis* (Type A *Ft.*), is the most virulent and is only found in North America [4]. It is associated with more serious syndromes such as pneumonic or typhoidal tularemia, with mortality rates in Northern America of as high as 24% [5]. The less virulent subspecies *Francisella tularensis* subsp. *holarctica* (Type B *Ft.)* is the main cause of tularemia in Europe, with

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Scandinavia and Eastern Europe being the most important endemic regions. About 800 cases are reported throughout Europe annually. Type B tularemia usually presents with milder symptoms in humans, but rarely pneumonic, disseminated, or mixed forms have been described [6]. The two other known subspecies, *Francisella tularensis* subsp. *mediasiatica* and *Francisella tularensis* subsp. *novidica,* are not clinically relevant.

The latest surveillance report of the European Centre for Disease Prevention and Control describes an increasing incidence of tularemia in Europe over the past 5 years [7]. We hereby present the first Belgian case of severe blood culture positive pulmonary tularemia, caused by the less virulent Type B *Ft.*

2. Case presentation

A 57-year-old male presented to the emergency department (ED) because of fever (38 °C), headache, myalgia, arthralgia and bilateral flank pain for a few days. He did not have respiratory symptoms. A SARS-COV-19 antigen self-test had been negative twice. Clinical examination in the ED was unremarkable (normal examination of the chest and abdomen, absence of lymphadenopathies, normal arterial blood pressure and normal oxygen saturation on room air of 96%). The patient had been previously healthy. He reported living in a wooded area with a variety of wild animals, getting about a dozen tick bites every year, and having been treated repeatedly with doxycycline for an erythema chronicum migrans.

Laboratory testing at presentation revealed a leukocytosis of 11.5 $\times$ 10^9/L (normal range 3.9–10.9 $\times$ 10^9/L) with 78% neutrophils, a minimal raise of AST and ALT (57 and 50 U/L resp., normal $<$40 U/L), and an elevated C-reactive protein (CRP) of 287 mg/L (normal $\leq$5.00 mg/L). On chest X-ray, only a small retrocardiac nodular density was seen. Because of the flank pain, a computed tomography (CT) scan of the upper abdomen was performed, which excluded abdominal abnormalities, but revealed several nodular lesions in both lower lobes with the presence of bilateral hilar and mediastinal adenopathies [Image 1]. Blood and urine samples were sent to the laboratory for culture. Influenza virus antigen test and SARS-COV-2 PCR were negative.

Atypical pneumonia was suspected, and antibiotic treatment was started with a combination of amoxicillin-clavulanate and clarithromycin intravenously. Despite this treatment, both fever (up to 40 °C) and CRP ($>$250 mg/L) remained high, without leukocytosis. *Legionella* urinary antigen test came back negative. A bronchioloalveolar lavage was performed, but cultures nor in-house real-time PCR for 29 respiratory pathogens could identify a causative bacterial, mycobacterial, viral, or fungal agent. Because of persistent high fever, endocarditis was excluded by transesophageal echocardiography, and because of potential environmental exposure, a broad serologic screening for zoonoses was initiated (including Q-fever, *Toxoplasma*, *Bartonella*, Leptospirosis, Hantavirus, *Borrelia burgdorferi*). Also, viral serology for human immunodeficiency virus (HIV), hepatitis B and C, Epstein-Barr virus (EBV), and Cytomegalovirus (CMV) were sent off. Only antibodies for *Borrelia burgdorferi* and EBV were positive, but results were consistent with an infection of older date. The empirical antibiotic treatment was then switched to a combination of intravenous ceftriaxone and doxycycline orally. Over the course of one week, fever and CRP started to lower, but unfortunately so did the oxygen saturation. A new CT scan of the lungs showed further extension of the infiltrates in both lower lobes and the development of a bilateral pleural effusion [Image 1]. Pleural drainage was performed, evacuating 1500mL of clear pleural fluid. Pleural fluid analysis was compatible with a lymphocyte-predominant exudate; no malignant cells were found. As no immediate causative pathogen was yet identified, further investigations were carried out. A 18F-fluorodeoxyglucose positron emission tomography CT (18F-FDG PET/CT) was scheduled.

Fever and biochemical inflammation started to improve one week after treatment with ceftriaxone and doxycycline. After almost 5 days of incubation, one of the blood cultures showed the growth of a gram-negative coccobacillus, identified as *Francisella tularensis* using matrix-assisted laser desorption-ionization (MALDI-TOF). Further testing at the reference laboratory with enzyme-linked immunoassay (ELISA) and PCR, both performed on blood and on the bronchioloalveolar lavage fluid, confirmed this diagnosis and identified the subspecies as *Francisella tularensis* subsp. *holarctica.* Intravenous gentamicin (at a dose of 5mg/kg once daily) was added to the treatment for a total duration of seven days. The 18F-FDG PET/CT scan showed FDG-captivating nodular densities spread across

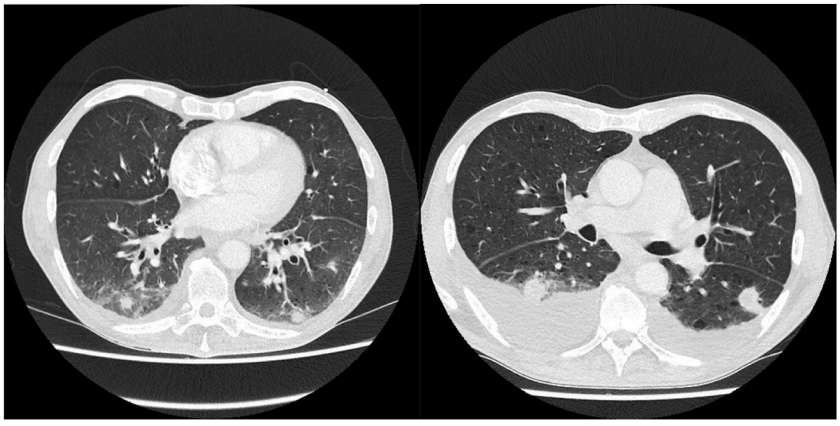

Image 1. Computed tomography (CT) of the chest at admission shows nodular infiltrates of the lower lobes (left). A CT-scan performed after one week shows progression of the nodular infiltrates and development of a bilateral pleural effusion (right).

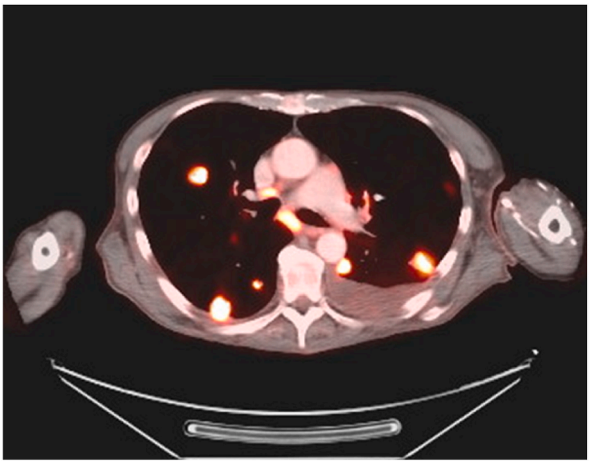

Image 2. a 18F-fluorodeoxyglucose positron emission tomography CT, performed after drainage of the right-sided pleural effusion, shows FDG-captivating nodular densities spread across the lungs and accompanying hilar, paraesophageal and mediastinal adenopathies.

the lungs and accompanying hilar, paraesophageal and mediastinal adenopathies, in the absence of other foci, compatible with pulmonary involvement by the identified microorganism [Image 2]. As tularemia is a notifiable disease in Belgium, the diagnosis was reported to the National Center for Disease Control. The patient was discharged after 15 days of hospitalization, with doxycycline 100 mg bid to complete a total treatment of 21 days. The patient made a full recovery without relapse.

3. Discussion

This case describes a rare form of disseminated pneumonic tularemia, which can present as a systemic febrile illness in the absence of obvious clinical abnormalities or a portal of entry. Pulmonary involvement by *Francisella tularensis* can be primary when caused by direct inhalation, or secondary due to hematogenous spread from another focus. Isolated bacteraemia is extremely rare with 1% in published series from Europe [6]. The exact mode of transmission in our patient remains elusive, although the most likely route seems the inhalation of contaminated dust: he lives in a wooded area where he frequently engages in forestal management activities that can produce aerosols. There was no history of direct animal contact, and although he reported several tick bites in his previous history, none occurred during the incubation period, so transmission via a vector or directly from an animal seems unlikely.

Given the infrequency of tularemia in Belgium, our clinical suspicion was low. We were lucky that the blood cultures became positive just within the usual 5-day cycle, thus allowing MALDI-TOF identification and subspecies determination, followed by the appropriate treatment of our patient. The diagnosis can easily be missed, not only because of the low incidence but also because of the variation in disease presentation, the nonspecific laboratory findings, and the difficulty to grow *Francisella tularensis* on culture. Several methods for rapid diagnosis of tularemia (e.g. immunohistochemistry, antigen detection, PCR, …) have been reported, but they all rely on prior clinical suspicion. The prerequisite of clinical suspicion also applies for serologic diagnosis, where repeat testing may be necessary because tests are usually negative at the beginning of the disease and become positive after two weeks (with increasing titers to up to 4–5 weeks).

Positive blood cultures are rare, even in severe disease, but have been reported for both *F. tularensis* subsp. *tularensis* and subsp. *holarctica* [8]. Whenever there is a suspicion of tularemia, the microbiology lab should be alerted. First of all to install necessary precautions to avoid transmission in the lab, but also to allow the use of supportive media and allow a longer incubation time of blood culture bottles, beyond the usual cycle of 5–7 days [9].

4. Conclusion

Pulmonary tularemia with or without bacteraemia remains rare. Given the increasing incidence, and as demonstrated by the present case, it seems prudent to include tularemia in the differential diagnosis of fever and pneumonia of unknown origin when an unfavorable evolution is seen with standard antibiotic treatment.

Declaration of competing interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2023.101882.

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