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Cervical lymphadenopathy in a patient receiving anti-TNF α treatment: glandular tuberculosis or oropharyngeal tularemia?

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ABSTRACT:

— ***Background:*** *Tularemia is a global anthroponotic disease that is endemic in some regions of Turkey, and it is carried by small rodents (hares) and arthropods (ticks, horseflies). Tularemia is caused by the* Francisella tularensis *bacteria, which is a facultatively intracellular Gram-negative bacillus.*

— ***Case presentation:*** *Herein, we present a case of oropharyngeal tularemia living in an endemic region of Turkey. The patient was 64 years old, had rheumatoid arthritis, and had been taking anti-TNF (adalimumab) in combination with methotrexate for about a year. She had swelling in her neck. She also had a sore throat and recurrent mouth ulcers. Her vital signs showed no abnormality; she had no fever, and physical examination only revealed hyperemia in the left cervical region and an enlarged painful lymph node. Significant tularemia serological titers supported the diagnosis, with contaminated water consumption being the most likely transmission route. Streptomycin (15 mg/kg/day, intramuscular) was given for 10 days. The patient healed completely without any complications. Six months later, there had been no recurrence.*

— ***Conclusions:*** *Particularly in endemic regions, tularemia should be considered in the differential diagnosis of lymphadenopathy with necrotic granuloma in patients receiving anti-TNF α treatment.*

— ***Keywords:*** Francisella tularensis*, Granulomatous lymphadenitis, Lymphadenitis, Oropharyngeal tularemia.*

INTRODUCTION

Tularemia is a rare zoonotic disease caused by the bacteria *Francisella tularensis*[1]. It can cause serious complications if not treated with appropriate antibiotic therapy. The causative agent enters humans *via* the respiratory or skin routes, eyes or mouth[1,2]. A small number of bacteria (10-50) can cause infection. Due to its virulence, the F. tularensis holartica subspecies is a potential agent of bacteriological warfare[2]. An upsurge in the number of human tularemia cases has recently been seen in numerous places worldwide and has largely been recorded in North America, Scandinavian countries, and Asian countries[3]. Vectors such as mosquitoes, horseflies, deer flies, and ticks spread the disease. Humans can contract the disease by directly contacting sick animals, eating infected animals, drinking, or coming into direct contact with polluted water, and inhaling bacteria-laden aerosols[4-6]. The clinical presentation differs depending on the exposure route[5,6]. F. tularensis can infect a wide variety of animals and be transmitted to people in a variety of ways, the most common being the bite of an infected arthropod vector (typically a tick) in the United States and Europe[7].

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Depending on the mode of transmission, the clinical manifestations have been classified as ulceroglandular, glandular, oculoglandular, pharyngeal, respiratory, and typhoidal tularemia[3,8]. The oropharyngeal form is caused by consuming contaminated food or water. Sore throats, mouth ulcers, tonsillitis, and swelling of the lymph nodes in the neck are all symptoms of oropharyngeal tularemia[4,7]. Tularemia caused by arthropods is typically an ulceroglandular form, characterized by ulceration at the site of pathogen inoculation through the skin, as well as satellite inflammatory lymphadenopathy[8]. The ulceroglandular form is the most prevalent (20-81%)[6,7]. Although the oropharyngeal form is seen at a rate of 1% worldwide, it is the most frequent clinical form of tularemia in Turkey, accounting for 77% of cases[8].

Tularemia is well recognized in immunocompetent (but poorly characterized in immunocompromised) individuals. Despite a lack of clear literature data on the specific features of this disease in immunocompromised patients, clinical reports[9] appear to reflect a distinct presentation of tularemia in these patients. The production of IL-12, tumor necrosis factor (TNF), and interferon (IFN) by phagocytic cells are required to initially control the Francisella infection. Based on these findings, it is highly likely that inhibiting one of these pro-inflammatory cytokines increases vulnerability to Francisella infection. Developments in immunopathology have enabled the creation of anti-TNF medications, which have brought substantial therapeutic advances in the management of rheumatologic illnesses, such as rheumatoid arthritis and ankylosing spondylitis[9,10].

Herein, we present a case of oropharyngeal tularemia, previously treated with methotrexate and adalimumab therapy for rheumatoid arthritis.

The 2013 revision of the Declaration of Helsinki's principles has been followed in this case study. The patient's informed written consent was acquired before this report was published.

CASE DESCRIPTION

A 64-year-old woman with rheumatoid arthritis who had been on adalimumab in combination with methotrexate treatment for about a year appeared with swelling in her neck. She also had a sore throat and recurrent mouth ulcers. In addition, there was an enlarged lymph node in the left cervical region (Figure 1). The lymphadenopathy grew in size over time despite the empirical amoxicillin clavulanate tablets (2x1 g/day for 10 days).

Her vital signs showed no abnormality; she had no fever, and physical examination only revealed hyperemia in the left cervical region and an enlarged painful lymph node. There was no inflammatory eschar. Hemogram parameters, routine inflammatory parameters [e.g., C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)], blood sugar, renal and hepatic functions, and electrolytes were all within normal ranges on the day of admission. Serologic testings for other infectious etiologies – such as Ebstein-Barr virus (EBV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), syphilis, toxoplasmosis, and brucellosis – were all negative.

Figure 1. Enlarged lymph node in the left cervical region.

Following surgical excision, histopathology showed epithelioid granulomas with large cells and central necrosis. Mycobacterial cultures had unfavorable outcomes. The clinical diagnosis of probable ulceroglandular tularemia was confirmed by the seroconversion (1/160 and 1/1,280 titers in acute and convalescent serum, respectively) with the microagglutination test (MAT). Significant tularemia serological titers supported the diagnosis, with contaminated water consumption being the most likely transmission route. Streptomycin (15 mg/kg/day, intramuscular) was given for ten days. The patient healed completely without any complications. Six months later, there had been no recurrence.

DISCUSSION

In a patient on anti-TNF alpha therapy, febrile lymphadenopathy with necrotic granulomas initially suggested tuberculosis (TB) reactivation[9]. However, the history of drinking polluted water and the inability to distinguish mycobacteria from various tissue samples prompted testing for a tick-borne illness, which ultimately resulted in the diagnosis of tularemia[9,10]. We discuss the potential connection between immunosuppression and the atypical infection's clinical course.

A significant proportion of tularemia patients admitted to medical centers experience fever, sore throats, and cervical swelling. Cervical masses, common in all age groups, are a clinically intricate and challenging condition that needs a systematic approach to achieve a differential diagnosis[11]. The most

common symptoms of oropharyngeal tularemia are severe throat discomfort with exudative pharyngitis or tonsillitis and ulcers. Such instances may resemble streptococcal tonsillitis, but penicillins or beta-lactam treatments have no effect. In addition, long-term lymphadenopathy in the cervical, parathyroid, and retropharyngeal regions can occur after febrile tonsillopharyngitis[11,12]. The patient in the presented case also had a sore throat and cervical swelling, nevertheless she had no fever or history of febrile disease.

Both infectious and non-infectious causes, such as malignancies, make differential diagnosis more important in etiology. However, when examining cervical masses, the patient's age should be considered. While inflammatory disorders are more common in younger age groups, malignancies are more likely in patients > 40 years old. The etiology of cervical masses in the age range between 16 and 40 years old, which includes our cases, is comparable to that of the pediatric age group. In this group, inflammatory disorders should be remembered first and foremost[11]. The presented case was 64 years old.

In our country, 52% of tularemia cases had been diagnosed mainly between December and March, with the oropharyngeal type caused by contaminated water being the most prevalent clinical presentation[12]. The woman in the presented case lived in a rural area and had a history of drinking possibly contaminated water, but she had no history of tick bites.

When tularemia is not suspected, these patients may receive a tissue biopsy or a fine-needle aspiration biopsy (FNAB). A histopathological or cytological study may rule out cancer. However, they may not be sufficient to distinguish infectious diseases. Histological analysis indicating crumbly (caseating) granulomatous lymphadenitis, for example, may be misdiagnosed as tuberculosis, particularly in endemic areas[13]. A study[11] about histopathology indicated granulomatous inflammation with or without necrosis. Other diseases with similar histologic findings include cat scratch disease, tuberculosis, sarcoidosis, and histoplasmosis[11].

Engin et al[14] reported 29 tularemia cases from Turkey. They discovered granulomatous lymphadenitis in three patients who had lymph node biopsies. They also found "casefying necrotizing granulomatous response" in the histological studies of these three patients, who had been previously misdiagnosed as having T-cell lymphoma (TCL)[14].

There is only a limited number[9,13,15] of similar patients in the available literature. Anti-TNF-α treatments reduce the bactericidal immune response against *Francisella spp*[9]. Also, according to patient reports[15], methotrexate can be given again once clinical symptoms have been controlled. Konstantinou et al[9] presented a case requiring long-term treatment with doxycycline and ciprofloxacin because of early relapse after ciprofloxacin was discontinued. They also reported that tularemia might progress more severely in patients receiving anti-TNF, which may be an indication for more effective treatment[9]. In our case, methotrexate treatment was discontinued and restarted at the end of treatment. The tularemia was treated with streptomycin (15 mg/kg/day for 10 days), and no relapse or complications were detected.

CONCLUSIONS

The diagnosis of tularemia is often made by clinical suspicion and testing serologically for tularemia. Tularemia should be considered in patients with risk factors for tularemia, cervical lymphadenopathy with or without oropharyngeal symptoms, and those unresponsive to beta-lactam antibiotic therapy. In addition, tularemia should be evaluated in the differential diagnosis of lymphadenopathy with necrotic granuloma in a patient taking anti-TNF α treatments, especially in endemic countries. Observational studies are required to investigate the association between immunosuppression and the clinical course of tularemia.

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Informed consent was obtained from the patient.

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