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A Suppurative Granulomatous Lymphadenitis Agent: Tularemia, Case Report

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ABSTRACT

Tularemia is a disease caused by a Gram-negative coccobacillus Francisella tularensis. The major clinical forms are ulceroglandular, glandular, oculoglandular, oropharyngeal, typhoidal, and pneumonic tularemia. Francisella tularensis, causes suppurative granulomatosus lymphadenitis. In this study, we wanted to report a case of oropharyngeal tularemia, which can be misdiagnosed as malignity, in a patient who presented with suppurative ganulomatous lymphadenitis.

Keywords: *francisella tularensis, tularemia, granulomatous lymphadenitis*

ÖZ

Süpüratif Granülamatöz Lenfadenit Etkeni: Tularemi, Olgu Sunumu

Tularemi Gram negatif bir kokobasil olan Francisella tularensis'in neden olduğu bir hastalıktır. Temel klinik formları ülseroglandüler, glandüler, okülоglandüler, orofaringeal, tifoidal ve pnömonik tularemidir. Francisella tularensis süpüratif granülomatöz lenfadenite neden olur. Bu çalışmada, malignite ile karışabilmesi nedeniyle, süpüratif granülomatöz lenfadenit ile prezente olan orofaringeal tularemi olgusunu sunmak istedik.

Anahtar kelimeler: *francisella tularensis, tularemi, granulomatöz lenfadenit*

INTRODUCTION

Tularemia is a disease caused by a Gram-negative coccobacillus Francisella tularensis [(1-3)]. It is transmitted to humans by arthropod and animal bites, contact with infected animal products, consumption of infected water or meat, aerosol droplets, or in the laboratory [(2)]. Due to the consumption of contaminated water and food most common form seen in Turkey and in other eastern European countries is oropharyngeal infection [(4)]. F. tularensis is an intracellular pathogen. It causes granulomatous and suppurative lesions especially in the affected regional lymph nodes and various organs [(5)]. Histopathological findings in affected lymph nodes have been found as ranged from well-defined acute inflammation and necrosis located within the outer cortex to generalized necrosis that obliterated the node with rare granulomatous inflammation [(6)]. We report a case of oropharyngeal tularemia in a patient who presented with cervical lymphadenopathy that can have similar clinical findings with metastatic carcinomas and lymphomas and we suggest to keep in mind cervical granulomatous lymphadenitis in differential diagnosis of cervical lymphadenopathies.

CASE

28-year-old, male patient was admitted to his family physician with fever, sore throat and dysphagia complaints in Bartın, Turkey. Antibiotic treatment was administered to him for one week (Ciprofloxacin 500 mg 2x1). In the following days, a mass gradually increasing in size, developed in his neck and after about 15 days he was admitted the outpatient clinic of otorhinolaryngology because of progressive enlargement of the mass. There were multiple lymphadenopathies with thickened cortical coats and without lipid echogenicity at all levels on the left side of the neck on Ultrasonography (USG), biggest ones being at the submandibular region with 21x12 mm, at anterior cervical region with 20x9 mm and at posterior cervical region with 23x10 mm. With these findings

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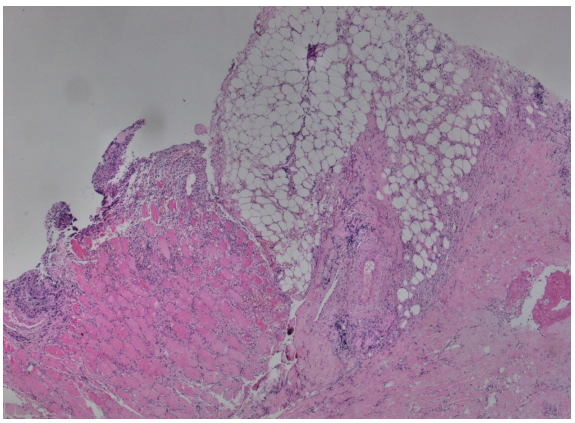

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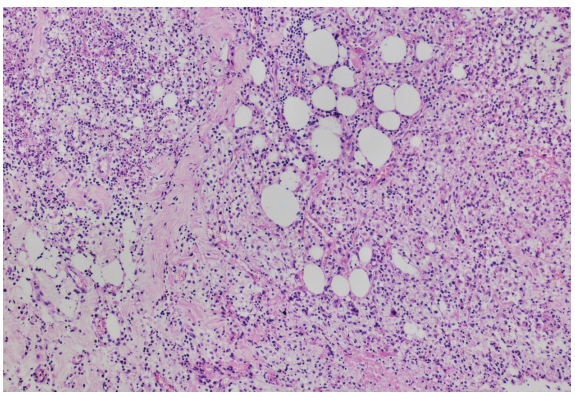

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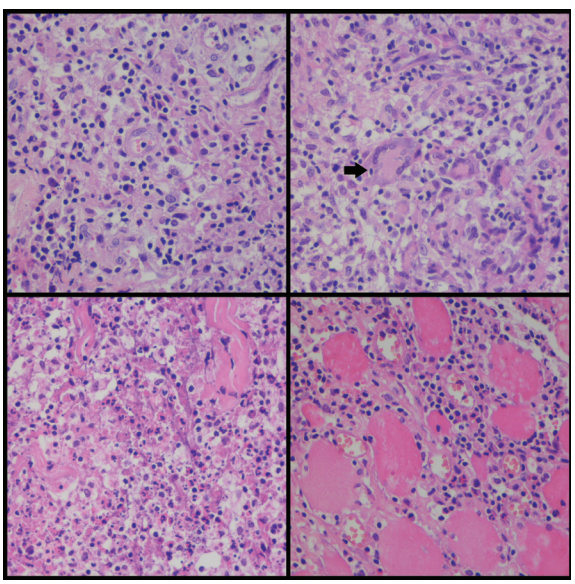

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Figure 1A. In a fibromusculoadipose stroma, heavy mixed inflammatory cell groups (H&E x40). B: Patches of abortive granulomas formations, some of which have epitheloid appearance of heavy histiocytic infiltrations and heavy mixed inflammatory cell groups resembling abscess (H&E x100). C. Mixed inflammatory cell groups and multinucleated giant cells (arrow shows) (H&E x400).

the patient was referred to İstanbul Okmeydani Training and Research Hospital, Otorhinolaryngology Clinic. On physical examination conducted in our clinic, there was a firm, immobile mass on left submandibular region. There was no erythema or drainage. Laboratory findings were as follows; WBC: 10.72/ mm^3, Hb: 14.42 g/dl, Hct: % 43.05 ESR: 69 mm/ H. On postero-anterior chest graphy there wasn't any specific lesion. Firstly, fine needle aspiration (FNA) biopsy was made with suspicion of lymphoma and carcinoma metastasis. On microscopic examination, it was nondiagnostic. There were squams and rare polymorphous nucleated leukocytes. Two days later, core biopsy was made and only striated muscle tissue was seen. After that incisional biopsy was made. On gross examination of biopsy material there were 3 incisional biopsy materials with the biggest one being 1.2x0.5x0.3 cm and the smallest one 0.5x0.4x0.2 cm. It was fixed with 10% formalin during routine tissue processing. Microscopic findings were, in a fibromusculoadipose stroma, patches of abortive granulomas formations, some of epithelioid appearance of heavy histiocytic infiltrations, rare multinuclear giant cells and heavy mixed inflammatory cell groups that resembling abscess (Figure 1A, B, C). We had to highlight the inflammatory infiltration of muscle fibers. On immunohistochemical study, CD68 was diffuse positive (Figure 2). CKPAN, CD79a and Pax5 were negatively stained (Figure 3). There was no sign of malignancy and Ehrlich Ziehl-Neelsen (EZN) test was negative for tuberculosis. We recommend to the case to be researched for infections with heavy histiocytic infiltration and systemic involvement. Patient admitted to infectious diseases clinic with initial diagnoses of Cat-Scratch-Fever, Kikuchi Fujimoto

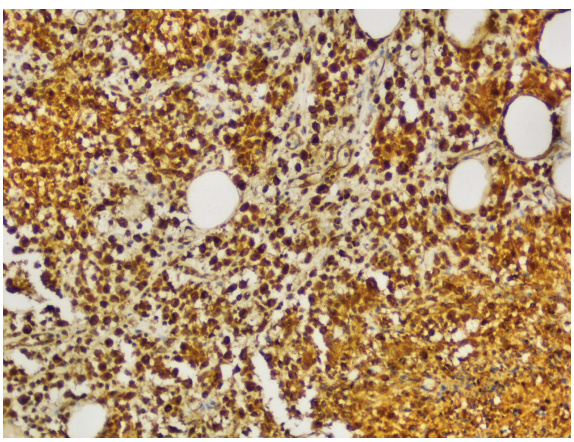

Figure 2. CD68 diffuse positive staining (x200).

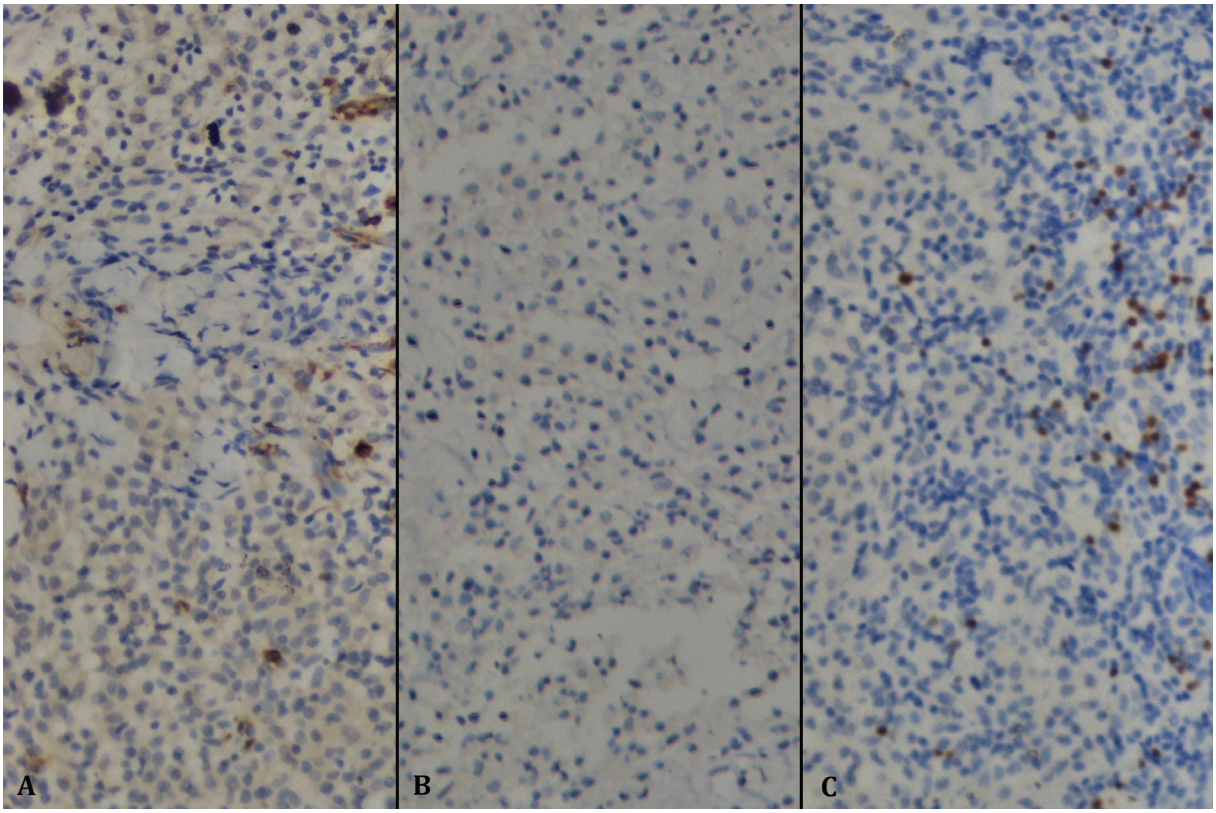

Figure 3. CD79a (A), CKPan (B), PAX5 (C) negative staining (x200).

Disease, Tuberculosis and Tularemia. PPD test was negative and on serologic test Tularemia antibody titer was 1/360 positive.

DISCUSSION

Tularemia outbreaks have been commonly reported in some areas of Europe, such as Sweden, Finland, Portugal, Spain, Kosovo, and Turkey [2]. Tularemia is a growing threat in Turkey, and there has been a rise in the number of reported cases, both epidemic and sporadic, from different regions of Anatolia [7]. Tularemia is seen most commonly in the Black Sea and Marmara regions of Turkey [4]. There are six clinical forms of Tularemia in humans: oropharyngeal, glandular, ulceroglandular, oculoglandular, pneumonic, and typhoidal [2,4,6,8]. Among all of the outbreaks in Turkey, the oropharyngeal form was the most common [2].

Common systemic findings found at the onset of disease in all forms are fever, chills, malaise, headache, cough, and myalgias [2]. The infection may also cause hepatitis, meningitis, pericarditis, sepsis and septic shock [3]. Enlarged lymph nodes, cervical and periauricular region being more frequently involved, are seen in nearly 85% of the cases. This can be the first and only sign of infection [7].

Lymphadenopathies caused by glandular or oropharyngeal tularemia may arise suspicion of malignancy. Those cases may undergo tissue biopsy or fine-needle aspiration biopsy, when tularemia is not kept in mind. In our case there were a gradually growing mass on neck site, and fever, sore throat and dysphagia complaints. It looked like tularemia but malignancy was not excluded. Histopathological or cytological examination may exclude malignancy. However, they may not be sufficient to differentiate infectious conditions [1].

Histologically lymphadenopathies are divided into three forms, abscess, abscess-granuloma and granuloma. In early phase, until the second week after infection, many lymph follicles appear and histiocytic cells gather in subcapsular sinus. Abscess with central necrosis and mononuclear cells is formed (Abscess form). From the second week to the sixth week after infection, several small epithelioid granulomas with central necrosis appear at the cortex and the pa-

racortex. These lesions fuse with each other and form irregular large lesions with central abscess (Abscess-granulomatous form). Several multinucleated giant cells also appear in the peripheral epithelioid cell layer. After the sixth week from infection, necrosis is homogenized and progresses to caseous necrosis in the center of the granulomatous lesion (Granulomatous form) [9]. In our case, cytologic aspiration was inadequate for diagnosis. Histopathological findings were patches of abortive granuloma formations, some of epithelioid appearance of heavy histiocytic infiltrations, rare multinuclear giant cells and heavy mixed inflammatory cell groups that resembling abscess that were favorable with suppurative granulomatous lymphadenopathies and EZN test was negative. In cities such as Bartın in Turkey where Tularemia is endemic, we took tularemia in our differential diagnosis. Routine laboratory tests are generally within normal range or non-specific. Culture of F. Tularensis is difficult; therefore, a definitive diagnosis of tularemia relies on clinical findings and antibody studies. Tube agglutination and microagglutination are used most commonly. However, detectable antibody response may take up to two weeks to manifest, and a diagnosis may not be possible with an agglutination test in the early stages of an infection [7]. An antibody titer of 1:160 or greater in a single specimen is diagnostic [2]. A diagnosis of tularemia was made in our patient after detection of F. Tularensis antibodies at a titer of 1/360 on an agglutination test.

The differential diagnosis includes toxoplasmosis; cat-scratch disease (CSD); mycobacterial, cytomegalovirus or Epstein Barr virus infection; streptococcal disease; and lymphoma or metastatic cancer [10].

Despite the fact that both oropharyngeal form of tularemia and streptococcal tonsillopharyngitis have common complaints like severe throat pain, exudative pharyngitis and/or tonsillitis differentiation between these entities is done by the response to the penicillins or beta-lactam antibiotics. While streptococcal tonsillopharyngitis responses dramatically to beta-lactam antibiotics tularemia does not [11].

Fine needle aspiration can be useful to confirm or exclude that lymphadenopathy may be due to a neoplastic lesion which is either primary or metastatic, or may be due to non-neoplastic processes. However, for the diagnosis of tularemia, FNA is not a useful method per se. FNA may raise the suspicion and should be supplemented by serology [6].

Infectious granulomatous lymphadenitis is classified as suppurative lymphadenitis and non-suppurative lymphadenitis. Differential diagnosis of suppurative granulomatous lymphadenitis in cervical lymph nodes mainly includes tularemia and CSD. The absence of the history of a cat-contact and a visible injury site on the skin helps excluding the diagnosis of CSD and also the identification of microorganism is necessary for the diagnosis [6].

The diagnosis of 'casseifying granulomatous lymphadenitis' is not sufficient to differentiate between tuberculous cervical lymphadenitis (TCL) and tularemia. The same histopathological features may be present in both of these diseases. The presence of casseifying necrosis, no neutrophils, and occasionally, intracellular and/or extracellular acid-alcohol-resistant bacilli in granulomas are the findings in TCL. On the other hand, the borders of granulomas in tularemia are not sharp and fewer giant cells are seen inside them [12].

In the literature, streptomycin is still the drug of choice. Other than streptomycin, gentamicin, tetracycline, chloramphenicol and more recently quinolones are also recommended [3]. In our case ciprofloxacin retreatment were given after Tularemia diagnosis and his complaints were regressed. Tularemia should be considered in the cases with fever, tonsillopharyngitis and cervical lymphadenopathy for the differential diagnosis, at least in suspected areas. If clinician suspect Tularemia with clinical findings, serological test will be useful before a FNA or a biopsy. Serological diagnosis will be comfortable for patient than an invasive attempt. After serological tests if there are no definitive results then biopsy must be taken with the clinical findings of the lesions that may be suspicious for malignancy.

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