Oropharyngeal tularemia mimicking tumoral relapse in a patient with Hodgkin lymphoma in remission

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Tularemia is a zoonotic disease caused by *Francisella tularensis*. The clinical forms mostly depend on the port of entry into humans. Ingestion typically results in the oropharyngeal form and is associated with symptoms such as fever, pharyngitis, cervical lymphadenitis, and suppuration. In this report, we describe a child treated for Hodgkin's disease presenting six years later with a left cervical lymphadenopathy mimicking a relapse.

Key words: Hodgkin lymphoma, lymphadenopathy, oropharyngeal, tularemia.

Tularemia is an anthropozoonosis, transmitted by small mammals (hares) and arthropods. The causative agent is *Francisella tularensis*, a non-capsulated, facultatively intracellular, Gram-negative coccobacillus. It is most common in the northern hemisphere, and outbreaks linked to ingestion of contaminated natural spring water have been described in western Turkey[1].

F. tularensis may enter the body from the skin, mucous membranes and the respiratory system. The clinical picture of the disease may vary depending on the route of exposure, the virulence of the microorganism and the immune condition of the host. Patients usually present with at least one of six classic types of tularemia: ulceroglandular, glandular, oculoglandular, pharyngeal, typhoidal, or pneumonic[1,2]. We report a case of oropharyngeal tularemia in a patient who presented with cervical lymphadenitis after being treated for Hodgkin's disease and achieving complete remission for six years.

Case Report

A 10-year-old girl was admitted to our hospital from Karabük due to a left cervical lymphadenopathy. She had been diagnosed with lymphocyte depletion classical Hodgkin's lymphoma stage IIA six years earlier and received five courses of combination chemotherapy consisting of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD). Her present complaints started 15 days earlier with signs and symptoms of lymphadenopathy. Physical examination showed an enlarged lymph gland conglomerate on the left posterior side of the neck, the largest of which was 4 cm in diameter (Fig. 1). Other physical examination signs were normal. Laboratory studies revealed: white blood cell count 9600/mm^3, hemoglobin 13.3 g/dl, platelet count 450000/mm^3, and erythrocyte sedimentation rate 25 mm/h. Serum electrolytes, kidney and liver function tests and chest X-ray were within normal limits. The serological tests for toxoplasmosis, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and rubella were negative. Ultrasound examination revealed multiple lymphadenopathies on the left-posterior neck. The largest lymph node was 36x29x15 mm and showed poor echogenicity. The patient was hospitalized and empirical treatment with broad-spectrum β-lactam antibiotics was started, but the patient's lymph nodes markedly increased in size over the next seven days. These findings were interpreted as relapse, and the patient underwent surgical excision. Histopathological examination showed

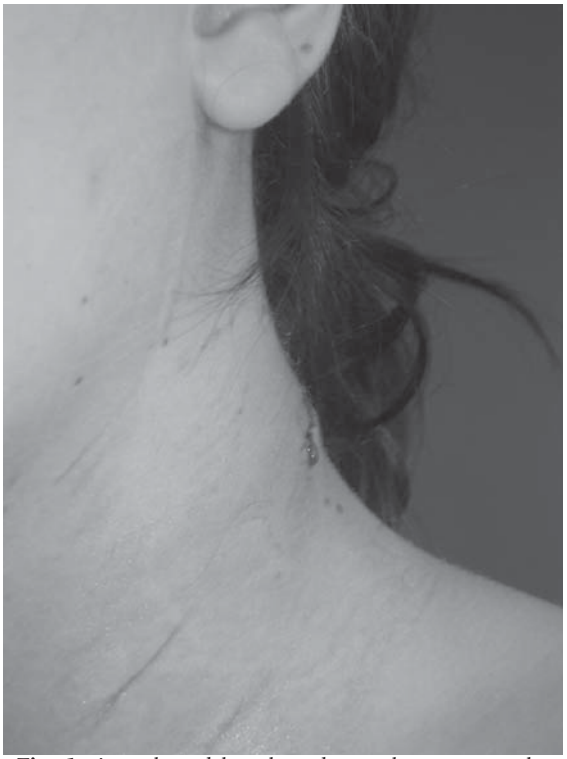

Fig. 1. An enlarged lymph node conglomerate on the left–posterior side of the neck of the patient.

nonspecific lymphadenitis, and culture of the drainage fluid was negative. Furthermore, as the patient had a history of living in an area where a tularemia outbreak was seen, the serum of the patient was obtained for tularemia microagglutination test. The serum antibody titer for *F. tularensis* was positive on serological examination (1/640). The diagnosis was confirmed by *F. tularensis* DNA amplification using polymerase chain reaction (PCR). On day 13, antibiotic treatment was changed to ciprofloxacin (30 mg/kg/day). The antimicrobial therapy was extended to three weeks, according to the clinical response of the suppurated lymph nodes. Four months later, no relapse had occurred. The patient has remained in continuous complete remission six years after the initial diagnosis of Hodgkin's lymphoma.

Discussion

Tularemia is a bacterial zoonosis disease that occurs primarily in the northern hemisphere. It usually presents with different clinical forms based on whether the infection is acquired through contaminated food or water. Most of the reported tularemia cases in Turkey in the last 20 years have been oropharyngeal and related to the consumption of contaminated water; other reports of cases from different European countries support this association[3]. Oropharyngeal tularemia is a rare but important differential diagnosis of streptococcal tonsillopharyngitis and cervical lymphadenitis not responding to β-lactam antibiotics. Tularemia may mimic other causes of lymphadenopathy, thus making the diagnostic process challenging for clinicians, microbiologists and pathologists[4]. The reappearance of an enlarged cervical lymphadenomegaly in our patient was first suspected to be a relapse of Hodgkin's lymphoma. The tularemia diagnosis will most likely be missed and appropriate therapy not prescribed if tularemia is not suspected for epidemiological reasons. Suppurating neck lymph nodes occurred in 40% of the cases in an outbreak of oropharyngeal tularemia in our country, where treatment was generally delayed[1,5].

Children have contracted the disease more often than adults, and several family members may be affected simultaneously. However, several studies reported that most tularemia patients were elderly. In Turkey, tularemia patients under 10 years of age have been extremely rare[6].

The diagnosis of tularemia ultimately rests on clinical suspicion. Results of routine laboratory tests, imaging features and pathological examination of the lymph nodes are nonspecific[2,5]. The microbiological diagnosis of tularemia relies mainly on serology. The tube agglutination test shows high sensitivity and specificity. Cross-reactions may only be seen with serum from patients with brucellosis and yersiniosis. A four-fold increase in the titer or a titer of agglutinating antibodies ≥1:160 confirms a clinical suspicion of tulatemia[4-7]. In our patient, a single titer ≥1:640 in the presence of a compatible clinical illness was accepted as tularemia. *F. tularensis* can be cultured from pharyngeal secretions, lymph node aspirates, blood and other patient specimens; however, it is only occasionally isolated from blood cultures. Physicians who suspect this infection should alert the laboratory to the need for special diagnostic and safety procedures[7, 8]. In our patient, *F. tularensis* was not isolated

from lymph node aspirates. Demonstration of bacterial antigen by immune assay and ribonucleic acid hybridization has been tried, without being widely applied, for the rapid diagnosis of tularemia. PCR-based methods have yielded highly promising results and will probably become more generally established in endemic regions[5].

Antimicrobials currently considered for treatment of tularemia are streptomycin, which has a clinical cure rate of 97%, and gentamicin and tetracyclines, which have rates of 88% and 86%, respectively[8]. Quinolones offer new options for the treatment of tularemia. European expert groups recommend quinolones as an effective treatment alternative. Reports on first-line treatment with ciprofloxacin in about 80 patients have shown a high efficacy[9-11]. We also successfully treated our patient with ciprofloxacin.

Oropharyngeal tularemia may be easily confused with other diseases that affect the cervical lymph nodes, such as streptococcus angina, tuberculosis, infectious mononucleosis, and lymphoma. This may lead to late diagnosis and inadequate treatment. Tularemia should therefore be considered in the differential diagnosis when cervical lymphadenopathy is involved[4,11,12].

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