Two cases of glandular tularemia from Turkey

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Tularemia is a bacterial zoonotic disease that is caused by *Francisella tularensis*. *F. tularensis* is transmitted to humans by handling infected animals, ingestion of contaminated food or water, inhalation of infective aerosols, and arthropod bites. Tularemia outbreaks have been commonly reported in some areas of Europe, such as Sweden, Finland, Portugal, Spain, Kosovo, and Turkey. Tularemia has six different clinical forms, depending on the route of transmission. In Turkey, the most common type is the oropharyngeal form. We present two cases of glandular tularemia with inguinal lymphadenopathy, which is an uncommon manifestation of this disease in our country. The patients were treated with gentamicin for 10 days and completely recovered. Glandular tularemia should be considered in the differential diagnosis of inguinal lymphadenopathy.

Key words: inguinal lymphadenopathy, tularemia, Turkey, Francisella tularensis.

Tularemia is a zoonotic infection caused by *Francisella tularensis*. Francisella is a small, aerobic, catalase-positive, pleomorphic, gram-negative coccobacillus. 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[1]. In Turkey, tularemia epidemics were believed to be waterborne for the following reasons: almost all of the cases are the oropharyngeal form; a few cases of oculoglandular and ulceroglandular tularemia were reported; only one mortality occurred due to tularemia, which indirectly suggests type B and waterborne epidemics; epidemics were limited to the same area in which people were using certain aqueducts without chlorination of the water system; and polymerase chain reaction positivity for F. tularensis was detected in the water from epidemic areas[2-4]. Two Turkish patients with glandular tularemia who had inguinal lymphadenopathy are reported here because of the rarity of this presentation in our country.

Case Reports

Case 1

In September 2010, a 17-year-old male presented to our hospital with swelling on the left groin. At that time, he had no other symptoms. However, he had fever and weakness 15 days before, and two days after these complaints, swelling in the right groin emerged. He had received non-specific antibiotic treatment with oral amoxicillin/clavulanate for five days. Other symptoms resolved but the swelling on the groin persisted. There was no history of genital discharge or dysuria. He was not sexually active. He was living in a village in Bala, a district in Ankara province, located in the central Anatolia region. On his physical examination, hepatomegaly 2 cm below the costal margin was detected. There was a painless enlarged mass on the left groin. The lesion measured 4×4 cm and there was no redness or warming of the adjacent skin. The rest of the physical examination was unremarkable. Laboratory examinations were as follows: hemoglobin 14 g/dl, white blood cell count 10,500/mm^3 with 52% polymorphonuclear leukocytes, 2% eosinophils, 38% lymphocytes, and 8% monocytes, platelet count 323,000/mm^3, C-reactive protein (CRP) level 3 mg/L, and erythrocyte sedimentation rate (ESR) 43 mm/h. Renal and hepatic function tests were normal. Urinary examination was normal. Human immunodeficiency virus (HIV) serology was negative. His Venereal Disease Research Laboratory (VDRL) testing was non-reactive. Serological tests for hepatitis A, B, C, Salmonella and Brucella were negative.

Inguinal ultrasound examination showed multiple lymphadenopathies on the left groin. The largest lymph node (36 x 15 mm) showed poor echogenicity with distinct hilus. Thickness and echogenicity of surrounding fatty tissue increased. Abdominal ultrasonography (USG) showed hepatosplenomegaly. Liver length was 14.9 cm; spleen length was 13 cm. Antibiotic treatment was started with ampicillin/sulbactam empirically. On the seventh day of hospitalization, antibody positivity for F. tularensis with a titer of 1/1280 was detected. The patient was diagnosed as glandular tularemia, and gentamicin treatment was commenced at a dose of 7.5 mg/kg/day intravenously. Ampicillin/sulbactam was stopped. A 10-day regimen of gentamicin therapy led to marked clinical improvement. The lesions progressively resolved and completely disappeared and the patient was discharged. At the last follow-up, in November 2010, he was well with no relapses of the inguinal mass. Antibody of *F. tularensis* was still positive with a titer of 1/1280. Follow-up abdominal USG showed that hepatosplenomegaly had resolved.

Case 2

In November 2010, a five-year-old boy, with no remarkable medical history, was admitted to our hospital with bilateral swelling on the groin. Twenty days before, the swelling in his groin appeared and became progressively larger. The adjacent skin became reddened and ecchymotic. He was prescribed amoxicillin clavulanate at the local hospital, but showed no improvement after a 14-day course of antibiotic therapy. He was living in a village in Corum, in the central part of Turkey, and he had a history of swimming in a valley. Physical examination revealed a painful lymphadenopathy on his right inguinal region measuring 2x1 cm, and a fluctuant mass measuring 3x4 cm on the left inguinal region with redness and warming of the adjacent skin. There was no other systemic involvement. Laboratory examinations were as follows: hemoglobin 12.4 g/dl, white blood cell count 12,500/mm with 30% polymorphonuclear leukocytes, 2% eosinophils, 60% lymphocytes, and 8% monocytes, platelet count 393,000/mm^3, CRP level 3 mg/L, and ESR 50 mm/h. Renal and hepatic function tests were normal. Urinary examination was normal. HIV serology was negative. Ultrasound examination showed a 24x8 mm lymphadenopathy with absence of hilus echogenicity on the right inguinal region and a 26x10 mm semisolid mass with dense content on the left inguinal region. Intravenous antibiotic therapy with ampicillin/sulbactam was started and percutaneous drainage was done. Bacterial culture of the drainage material was negative. As the initial presentation symptoms of the patient were an inguinal mass and lymphadenopathy that did not respond to beta-lactam antibiotics, tularemia was considered in the differential diagnosis. On the fifth day of hospitalization, antibody positivity for F. tularensis with a serum titration of 1/320 was detected. Based on the clinical and serological findings, glandular tularemia was diagnosed. Treatment was changed to intravenous gentamicin (7.5 mg/kg per day), and the lesions progressively resolved. After gentamicin treatment was completed to 10 days, the patient was discharged. At the last follow-up, in October 2010, the inguinal mass and lymphadenopathy had disappeared completely. Antibody of *F. tularensis* was still positive with a titer of 1/160. The follow-up ESR was 25 mm/h.

Discussion

F. tularensis is a zoonotic infection that is mainly seen in the northern hemisphere. Arthropods (ticks, deer flies) are the main transmission vectors, and small animals (rabbits, hares, muskrats) serve as reservoir hosts in the terrestrial life cycle. In the aquatic life cycle, muskrats, beavers, and voles shed live *F. tularensis* into their aquatic habitat, where humans come into contact with the organism. The infectious dose can be as low as 10 bacterial cells for type A organisms[1]. There are two virulent subspecies of *F. tularensis*: *F. tularensis* tularensis (type A) and *F. tularensis holarctica* (type B). The highly virulent type A occurs only in North America, whereas the less virulent type B is found in North America, Europe and Asia[5].

Several outbreaks of tularemia have been reported from Turkey since 1936. Between 1936 and 2004, 507 tularemia cases were described in Turkey. Tularemia was instated in the list of nationally notifiable diseases in 2005, and from this time to 2010, approximately 1300

cases were reported. Studies have shown that outbreaks were waterborne in our country. Although before 2005, tularemia was commonly seen in Marmara and the western Karadeniz region, between 2009 and 2010, new tularemia cases were reported from other regions, especially the central Anatolia region[6]. The present cases came from the central Anatolian region of Turkey.

Tularemia has six clinical forms in humans: ulceroglandular, glandular, oropharyngeal, oculoglandular, pneumonic, and typhoidal. Although ulceroglandular and glandular tularemia may comprise more than 95% of the outbreaks in Sweden, Finland, and the United States, in eastern European countries, particularly in Kosovo, Bulgaria and Norway, oropharyngeal tularemia is the most common type[7,8]. For all of the outbreaks in Turkey, the oropharyngeal form was the most common[2,6,9,10]. The distinction between the clinical forms depends on the involvement of skin or mucous membranes and localization of the associated lymphadenopathy[1]. Acquisition of the bacteria through skin (ulceroglandular, glandular forms) or via oral (oropharyngeal form) or eye mucous membranes (oculoglandular) usually results in a significantly enlarged tender regional lymphadenopathy. The regional nodes further enlarge, necrose and may rupture. When bacteria are inhaled, the infection will result in deep lymph node enlargement[5]. The ulceroglandular and glandular forms mainly affect the head and neck region. In ulceroglandular forms, the typical skin lesion begins as an erythematous papule or nodule that indurates and ulcerates with associated enlarged, tender lymph nodes. Glandular tularemia represents essentially the same process as ulceroglandular disease, except that a skin lesion either healed before presentation or was minimal or atypical and overlooked[11]. Our patients had unilateral inguinal lymph node enlargement without ulceration and there were no skin lesions. These findings led to the consideration of glandular tularemia. In Case 2, there was a history of swimming in the valley, which is considered an aquatic transmission route. Although there was no known epidemiological risk factor in the history of Case 1, he was also living in a rural area. It was reported that in 25% to 50% of tularemia patients, the source of infection was not evidenced[11]. The portal entry of the bacteria for glandular tularemia is skin, but it could not be detected in either of our patients. We think that the local lesions of our patients might have healed by the time the patients presented for medical attention. The median incubation time is 3 to 5 days (range: 1–21 days)[5]. Systemic findings such as fever, headache, malaise, chills, headache, cough, and myalgias were present in all forms at the onset of disease. These findings were present only in the history of Case 1, but were not determined in Case 2. At presentation, both patients had inguinal lymphadenopathy without fever or other findings. Systemic symptoms may resolve by the time medical help is sought, so that the clinical picture is dominated by the isolated lymphadenopathy, leading to many efforts in the differential diagnosis. Enlarged lymph nodes may persist for prolonged periods, and in some patients, an exposure or prior febrile illness will be forgotten. For this reason, tularemia may not be considered in the initial differential diagnosis of some patients whose primary presentation is lymphadenopathy[11]. The differential diagnosis of inguinal lymphadenopathy should include lymphadenitis due to urinary tract infection, suppurative infections of the lower extremities, lower abdominal wall or perineum, venereal disease, plague, tuberculosis, cat-scratch disease, malignancy, and tularemia[5,12]. Our patients had inguinal lymphadenopathy without ulcers. Case 1 was a sexually inactive adolescent, and Case 2 was a child. Both patients had unilateral inguinal lymphadenopathy and negative HIV serology, and Case 1 had a nonreactive VDRL test. For these reasons, we excluded venereal diseases. Inguinal lymphadenopathies of the current patients were nonsuppurative, and there were no clinical findings that associated tuberculosis disease or history of cat scratch. USG findings of our patients were indicative of an infectious lymphadenitis. Inguinal lymphadenopathy is included in the differential diagnosis of tularemia. Although inguinal lymphadenopathy was reported in up to 30% in some series from North America, where the most common form of disease is ulceroglandular or glandular, to our knowledge, it had been reported from Turkey in only one article and only one case[10,13-16]. This may be related to the fact that the oropharyngeal form is the most common form of tularemia in our

country. In our own series of 38 tularemia cases, there were 32 oropharyngeal, 2 glandular and 2 oculoglandular tularemia cases. Two cases presented only with erythema nodosum (unpublished data).

Routine laboratory tests are generally within normal range or non-specific. There is usually no significant increase in CRP and ESR. 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. An antibody titer of 1:160 or greater in a single specimen is diagnostic. Agglutinating antibodies begin to rise approximately 14 days after exposure, peak in 4 to 5 weeks, and remain detectable for 10 to 30 years after infection. Enzyme-linked immunosorbent assay is also used for the diagnosis. In the pathological examination of the tularemia lymph nodules, lesions are characterized by the presence of histiocytes, macrophages, lymphocytes, and giant cells in addition to areas of necrosis[11,17]. Both of our patients were diagnosed with high titers of specific antibodies.

Drugs used empirically in many cases of lymphadenitis of uncertain origin, like cephalosporins, amoxicillin/clavulanate and macrolides, are not effective against tularemia. Doxycycline, fluoroquinolones and aminoglycoside are effective antibiotics. The therapy usually lasts 7 to 14 days. Treatment is accepted to be successful if the signs and symptoms disappear and if the involved lymph nodes decreased in size without suppuration[1,9,11]. Delay in the diagnosis and specific treatment was an important risk factor for treatment failure. Our patients were given gentamicin for 10 days, and both of them recovered completely without relapse.

Although the predominant form in Turkey is oropharyngeal, tularemia should be considered in the differential diagnosis of patients with inguinal mass and lymphadenopathy that are resistant to the treatment with beta-lactam antibiotics. Epidemiological findings play a major role in supporting the early clinical diagnosis and effective treatment of tularemia.

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