A rare cause of abdominal lymphadenopathy–tularemia: report of two pediatric cases

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Tularemia caused by *Francisella tularensis* occurs worldwide in the northern hemisphere, with great variation in geographic and temporal occurrence. It generally presents as an acute febrile disease with the major clinical presentations including the six classic forms of tularemia: ulceroglandular, glandular, oculoglandular, oropharyngeal, typhoidal, and pneumonic. In contrast to European countries, where the ulceroglandular form is more prominent, the oropharyngeal form is the most common presentation in Turkey. We present rare cases of oropharyngeal tularemia in a 16-year-old boy and nine-year-old girl. To the best of our knowledge, these are the firstly described abdominal lymphadenopathy cases from Turkey. The second case was admitted with erythema nodosum, and abdominal lymphadenopathy was detected during the investigation. Excisional lymph node biopsy revealed abdominal tularemia. It is necessary to consider tularemia in the differential diagnosis of abdominal lymphadenopathy in tularemia regions. We also conclude that oropharyngeal tularemia can cause lymphadenopathy in any part of the gastrointestinal tract.

Key words: abdominal lymphadenopathy, tularemia, children.

Tularemia, caused by the facultative intracellular Gram-negative bacterium *Francisella tularensis*, is a multisystemic disease in humans and some animals[1]. It is found in a wide range of animal reservoir hosts throughout most areas of the northern hemisphere[1,2]. The clinical picture and severity of the disease in humans vary depending on the portal of entry, virulence of the particular organism, and immune status of the host. Clinical presentations include the six classic forms of tularemia: ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, and typhoidal[3]. In the international literature, the most common transmission route of tularemia is exposure to infected animals or ticks, whereas in Turkey, the main mode of transmission of *F. tularensis* is considered to be drinking unchlorinated water or uncontrolled spring water[3]. Diagnosis of tularemia is challenging because patients admit to the clinics mostly with persistent cervical lymphadenopathy and are diagnosed/treated as tuberculous lymphadenitis. We present the rare case of oropharyngeal tularemia with abdominal lymphadenopathy in a 16-year-old boy and nine-year-old girl. The second case was admitted with erythema nodosum, and abdominal lymphadenopathy was detected during the investigation. Excisional lymph node biopsy revealed abdominal tularemia.

Case Reports

Case 1

A 16-year-old previously healthy boy admitted to our clinic with abdominal pain lasting for approximately one month. The patient's history revealed that he visited rural areas frequently and drank natural spring water during these visits. At the time of onset of the abdominal pain, he also had tonsillitis. The physical examination showed only mild tenderness of the right lower quadrant of the abdomen. Complete blood count and serum biochemistry parameters were normal. There were no atypical

cells on his peripheral blood smear. Acute phase reactants were slightly elevated (erythrocyte sedimentation rate (ESR): 30 mm/h, serum C- reactive protein (CRP): 0.36 mg/dl). His blood lactate dehydrogenase level (LDH) was 940 U/L and tuberculin skin test (TST) 10x10 mm, and salmonella and brucella serology were both negative. Furthermore, there were no pathological antibody titers against *Toxoplasma gondii*, *Yersinia enterocolitica* or *Y. pseudotuberculosis*. Occult blood was negative in stool. Abdominal sonography showed conglomerated lymph nodes on the right side of the abdomen, with central anechoic parts, and the dimension of the largest lymph node was 42x22 mm in diameter. Abdominal tomography revealed pathological lymph nodes (largest dimension 34x31 mm) with centrally located hypodense areas (necrotic?) and showing patchy nodular contrasts. An excisional lymph node biopsy was performed. Microscopic investigation showed necrotizing granulomatous lymphadenitis, indicative of an infectious origin. The histological picture resembled tuberculosis; therefore, Ziehl-Neelsen staining and polymerase chain reaction (PCR) analysis for mycobacteria were performed. Both were negative for tuberculosis. Periodic acid-Schiff and Grocott staining of the histopathological specimen ruled out fungal infection. Because the patient resided in a tularemia endemic region, tularemia serology was performed, and his tularemia serology was positive, as 1/640 titer. Treatment with doxycycline and gentamicin was started, but as there was no improvement in the abdominal lymphadenopathy, the antibiotic treatment was switched to ciprofloxacin. After 14 days of ciprofloxacin treatment, his LDH level decreased to 236 U/L, CRP decreased to 0.18 mg/dl, and ESR decreased to 11 mm/h. He had no abdominal pain, and the sonography showed regression of the lymph nodes. During the one-year follow-up, there was no relapse in his complaints or the tularemia. Microagglutination test (MAT) was found to be 1:160.

Case 2

A nine-year-old girl admitted to our center with bilateral erythema nodosum. Her medical history revealed that antibiotic therapy was started 10 days ago with the diagnosis of tonsillitis, and erythema nodosum developed on the seventh day of the therapy. She had erythema nodosum on her tibia bilaterally; hepatosplenomegaly was not identified. ESR and CRP were 50 mm/h and 4 mg/dl, respectively. Abdominal sonography and abdominal computed tomography showed multiple conglomerated lymphadenopathies (35x20 mm) on the right lower quadrant and multiple paraaortic, parailiac, femoral lymphadenopathies, measuring 22x8.5 mm in greatest diameter. Laparoscopic lymph node excision was performed for the etiology. Pathological evaluation confirmed necrotizing lymphadenopathy. No acid-fast bacteria were observed in lymph node aspirates, and none of the samples was positive for *Mycobacterium tuberculosis* by PCR or in culture. Periodic acid-Schiff and Grocott staining of the histopathological specimen ruled out fungal infection, and tularemia PCR was negative. The patient's family noted that they were living in a province in which tularemia is endemic in its districts and rural areas. A review of the patient's records and interviews with family members disclosed a history of natural spring water consumption one week before admission, but there was no recall of tick bites or animal contact, and her first cousin had a history of oropharyngeal tularemia. Titers of antibody to *F. tularensis* determined on the 5th day of hospitalization were 1:640. She was diagnosed as oropharyngeal tularemia, and gentamicin therapy was initiated. After 14 days of gentamicin, her lymph nodes had regressed and no relapse occurred. Titers of antibody to *F. tularensis* determined on day 7 of hospitalization were 1:640, and ciprofloxacin treatment was administered with the diagnosis as tularemia. During her treatment in our hospital, erythema nodosum developed on both of her mother's legs coincidentally, and her tularemia serology was positive, as 1/320 titer.

Discussion

Tularemia is a zoonotic disease caused by the Gram-negative bacterium, *F. tularensis*. It is transmitted from animals to man through arthropod bites, direct contact with infected animals, ingestion of contaminated food and water, and inhalation[4]. Six forms have been defined: ulceroglandular, oculoglandular, pneumonic, oropharyngeal, gastrointestinal, and typhoidal. Although ulceroglandular type tularemia is the most common type in the literature, the oropharyngeal type is more

common in Turkey[5,6]. Oropharyngeal and gastrointestinal tularemia may develop after oral exposure, potentially from ingestion of contaminated meat or exposure to infected water[7]. The main mode of transmission of *F. tularensis* in Turkey is presumably waterborne[8]. The enlargement of mesenteric lymph nodes frequently causes abdominal pain in children, being an indication for laboratory investigations. Acute diarrhea, appendicitis, diverticulitis, *Y. enterocolitica* infection, human immunodeficiency virus (HIV) infection, Mycobacterium avium complex (MAC), tuberculosis, inflammatory processes (i.e. familial Mediterranean fever (FMF), Crohn disease, ulcerative colitis, connective tissue diseases), and malignant disease can cause mesenteric lymphadenopathy. Tularemia is a rare cause of abdominal lymphadenopathy in children[9].

The primary clinical forms of tularemia vary in severity and presentation according to the virulence of the organism, infectious dose, site of inoculum, and immune status of the host[3]. The disease can take a variety of clinical forms, from the severe generalized form, through glandular variants, to subclinical cases fortuitously diagnosed by serology[3]. Pharyngeal tularemia, another variant of ulceroglandular disease, is the result of primary invasion through the oropharynx due to ingestion of contaminated foods or water or contaminated droplets[3]. The oropharyngeal form of tularemia, which represents a few cases overall in the United States and Europe, has been seen with increasing frequency in recent outbreaks in Turkey and is responsible for more than 94% of cases of tularemia in Turkey[3]. After oral intake of infected water or food, lesions develop primarily in the oropharynx (tonsillitis and pharyngitis) and draining lymph nodes, throughout the gastrointestinal tract, or there may be few lesions. Patients present with a sore throat and/or abdominal pain due to mesenteric lymphadenopathy[7]. Most of the oropharyngeal tularemia cases had preauricular, submandibular or anterior cervical lymphadenopathy[10]. A search of the PubMed Medline to identify reports on mesenteric lymphadenopathy with oropharyngeal tularemia in the literature revealed only one case, reported from the Czech Republic in 1967[8]. Additionally, to the best of our knowledge, the two cases reported herein are the first detailed accounts of oropharyngeal tularemia with abdominal lymphadenopathy in Turkey.

Primary and secondary cutaneous lesions can be seen in tularemia. While primary lesions are mostly associated with route of transmission, secondary lesions (tularemids) are related to systemic dissemination[1]. Secondary skin rashes such as diffuse maculopapular and vesiculopapular eruptions, pustules, erythema nodosum, erythema multiforme, acneiform lesions, and urticaria may be found in up to 43% of tularemia cases[11,12]. They usually appear within the first two weeks of symptoms, and rash is more common in women than in men[11,12] . After papular and papulovesicular eruptions, erythema nodosum is the second most common secondary skin manifestation, occurring in 1–13% of cases[11,12]. The lesions appear at the end of the second week of illness, primarily on the legs, but occasionally on the arms, and typically take two weeks to resolve[13]. To the best of our knowledge, this is the first abdominal tularemia case presenting with erythema nodosum. Serology is the cornerstone of diagnosis in tularemia since the culture requires special media and a level 3 biocontainment facility. Antibodies to *F. tularensis* may be demonstrated by agglutination (tube, microplate and hemagglutination), indirect immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA), and western-blot (WB)[3]. The MAT remains the most common method used to detect antibodies against *F. tularensis* and is considered as the current reference method for the serodiagnosis of tularemia. In the presence of compatible symptoms, sustained high tube agglutination titer of ≥1:160 or MAT titer of ≥1:128 in an acute specimen supports a presumptive diagnosis of tularemia[3]. Definitive serologic diagnosis requires a four-fold or greater rise in titer between acute and convalescent samples since an equivocal titer may be due to cross-reactive antibodies, past infection, or very recent infection[3].

Francisella tularensis is generally susceptible to a range of antibiotics, including fluoroquinolones, streptomycin, and gentamicin, and treated patients have a favorable prognosis. Tetracycline, doxycycline, and chloramphenicol may be used but are bacteriostatic, and treatment must be provided for 14-21 days to prevent a relapse. *F.*

tularensis produces a beta-lactamase and is not susceptible to penicillin-class drugs and first-generation cephalosporins[13,14]. The differential diagnosis of tularemia is extremely broad. Granulomatous infections, i.e. tuberculosis, sarcoidosis, cat scratch disease, brucellosis, lepra, leishmaniasis, histoplasmosis, paracoccidiosis, and lymphogranuloma venereum mimic tularemia. Among these diseases, tuberculosis is the most commonly misdiagnosed disease in tularemia[13,14].

In light of this very rare presentation of tularemia, it is necessary to consider tularemia in the differential diagnosis of abdominal lymphadenopathy in tularemia regions. We also conclude that oropharyngeal tularemia can cause lymphadenopathy in any part of the gastrointestinal tract.

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