A Disease to Remember in Differential Diagnosis of Granulomatous Lymphadenitis: Tularemia

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Abstract

Tularemia is a zoonotic disease caused by *Francisella tularensis*. In the recent years, tularemia has become a reemerging infection in Turkey, with epidemics and also sporadic cases. The histopathology of tularemia is similar with tuberculosis. Thus, tularemia should be considered in the differential diagnosis of chronic granulomatous diseases. In this article, we presented a case of a 12-year-old girl with tularemia who applied to another health center with cervical lymphadenomegaly and treated as tuberculous lymphadenitis after the determination of granulomatous lymphadenitis. *(J Pediatr Inf 2015; 9: 81-4)*

Keywords: Tuberculosis, granulomatous lymphadenitis, tularemia

Introduction

Tularemia is a zoonotic disease caused by *Francisella tularensis* usually with a course of fever and lymphadenopathies (1). It is most frequently transmitted via the water and food contamination caused by such rodents as mouse, rabbit, squirrel and beaver as well as via the vectors such as ticks and flies. Transmission through tick in summers and through animals, contaminated water and food in winters is more frequent (2). While mosquito and tick bites are the most frequent ways of transmission in Europe, the most frequent way of transmission in our country is the use of contaminated water. The disease in Turkey has been extensionally moving from northwest to the eastern and southern regions (3).

F. tularensis spreads through the regional adenoids in the body; it causes lymphadenopathy and/or spreads out to the distant organs through bacteremia. In cases with surgical excision, it requires a comprehensive differential diagnosis to report the samples as granulomatosis reaction. The infectious factors such as mycobacteria, brucellosis, toxoplasmosis and cat scratch disease, idiopathic etiologies such as sarcoidosis, crohn disease and primer biliary cirrhosis, exposure to chemical substances such as mineral oils, talk and silica, and malignities such as lymphomas, carcinoma, dysgerminoma frequently cause granulomatosis lympodenopathy (4). Since the changes caused by tularemia in the lymph node biopsy are in the shape of granulomatous lymphadenitis prevalent together with caseous necrosis, the tularemia cases are often diagnosed as tuberculosis (TB) (5).

In this article, a case of tularemia that applied to another health center with cervical lympadenomegaly and treated as a tuberculous lymphadenitis after the determination of granulomatous lymphadenitis was presented.

Case Report

The 12-year-old female patient who lived in a village of Merzifon town in the province of Amasya presented with our hospital due to swelling complaint on the right neck lasting for four months. In the physical examination, there was no specificity in the right cervical region except, 5x6 cm sized lymphadenopathy with soft consistency and right tonsil hypertrophy.

Three months before her history, it was learnt that she presented with another health center with same complaint in Istanbul and in the cervical tomography (BT) taken there, lymphadenopathy was found and therefore, it was investigated.

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The thorax BT and quantiferon tests of the patient done in the same health center were found normal; as non-necrotizing granuloma was found as a result of the fine-needle aspiration biopsy (FNAB), the patient was commenced with 4 drugs anti-TB treatment (isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 35 mg/kg, ethambutol 20 mg/kg) with the diagnosis of lymphadenitis. It was learnt from the patient's history that fever was never monitored and there was no complaints of redness or discharge on the lymphatic gland. Despite the 2-month-long regular treatment with appropriate doses, the patient presented with our hospital upon the continuing complaints and the following findings were obtained in the physical examination; overall good condition, body temperature was 36,3 °C, respiratory rate 18/minutes, pulse 96/minutes, and blood pressure 115/80 mmHg. In the laboratory tests, it was found that white blood cell count was: 6200/ mm^3 (4000-11000/mm^3), erythrocyte sedimentation rate: 7/hour (0-20 /hour), C –Reactive Protein: 15 mg/l (0-5 mg/l). There was no specificity in the biochemical parameters. *Salmonella, Toxoplasma, Brucella,* CMV, EBV, HAV, HBV, HCV and HIV serologies were negative. Chest radiography was normal. In the cervical CT taken in our hospital, the lump lesion image showing liquefaction was considered as compatible with suppurative lymphadenitis. In the detailed anamnesis, it was learnt that 20 people in the patient's village recently had operations on the swelling on their necks, no health screening was carried out reading this problem and no measures were taken. The patient took her tularemia microagglutination tests with the provisional diagnosis of tularemia to the Tularemia Reference Center at Uludağ University. Before the microagglutination test results came out, with the provisional diagnosis of oropharyngeal tularemia and secondary abscess, the patient was given streptomycin (30 mg/kg/day, 2 doses, im) and ampicilin-sulbactam (200 mg/kg/day, 4 doses iv) and anti-TB treatment was discontinued. Upon the detection of reduction in the lymphatic gland on the 10th day of treatment, drainage was implemented by the Ear Nose and Throat (ENT) department. In the follow-up, ampicilin-sulbactam treatment was stopped on the 14th day; and as minimal reduction was observed in the size of the mass on the 20th day, drainage was implemented again by the ENT. Patient's treatment was changed as doxycycline 2, 2 mg/kg/dose (2x100 mg). As the patient was observed to have a clear reduction in the size of the mass on the 7th day, the patient was called in for policlinic control and then discharged. Doxycycline treatment was completed and discontinued on the 14th day. As the patient's microagglutination test result was found positive at 1/640 titer on the 2nd week of her hospitalization, the Provincial Health Directory was notified. The water samples taken from the village of the patient for *F. tularensis* polymerase chain reaction (PCR) were sent to the Turkish Public Health Agency.

Table 1. Tularemia epidemics in Turkey between 1936-2005*

Year	Province	Case	Season	Transmission
1936	Lüleburgaz	150	Summer	Waterborne
1937	Tatvan	6		Food
1945	Lüleburgaz	18	Spring	Waterborne
1953	Antalya	200	Autumn	Waterborne
1988-2002	Bursa	205	Winter	Waterborne
1997	Ankara	16	Winter	Waterborne
2000	Düzce	21	Autumn	Waterborne
2001	Bolu	14	Autumn	Waterborne
2002	Balıkesir	115	Winter	Waterborne
2004	Suluova	43	Autumn	Waterborne
2004-2005	Zonguldak	61	Winter	Waterborne
2004-2005	Kocaeli	145	Winter-Spring	Waterborne
2004-2005	Kars	56	Winter-Spring-Autumn	Waterborne
2005	Kocaeli	129	Winter	Waterborne
2005	Tokat	8	Winter	Waterborne
2005	Edirne	10	Winter	Waterborne
2005	Düzce	11	Winter	Waterborne

*Obtained from Source 1

Discussion

Tularemia is a zoonotic disease whose frequency is gradually increasing. The recurrence of tularemia cases may depend on climate, environmental changes, changes in human activities to a lesser degree, local and regional wild life and changes in the vector population (3). The very first tularemia diagnosis was made in 1920s in the Thrace region in our country followed by sporadic cases and small scale endemics in the following years (6). The biggest epidemic in Turkey was seen in Antalya with more than 200 cases in 1953. According to the data of the Ministry of Health, a total of 428 cases were reported in 2009 in our country; according to the 2010 data, there were 117 cases in the province of Yozgat, 89 in Kütahya and 32 cases in Çankırı (1). Tularemia has been considered as a notifiable disease (Group C disease) since 2005 in Turkey. Table 1 presents the tularemia epidemics in Turkey between 1936 and 2005 (1).

Although culture positivity is the golden standard in the diagnosis of tularemia, as the virulence and laboratory-based transmission risk is high, serologic tests are usually used for the diagnosis of the disease. Out of culture methods usually are agglutination test, immunoassay and PCR-selected differential diagnosis. Antibodies are seen to become positive usually within 6-10 days (7).

Figure 1. The existing cervical lymphadenopathy in our case

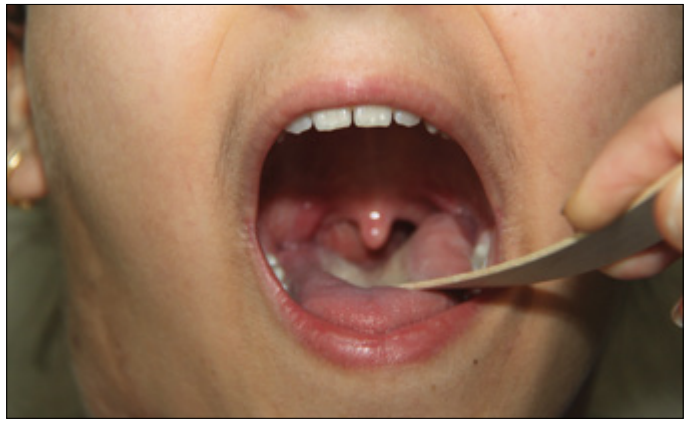

Figure 2. Oropharyngeal tularemia image in our case

In tularemia, non-necrotic reactive changes are histopathologically detected in the early period. From second week on, abscess formation seen together with epithelioid cells, and from fourth week on, caseous necrosis, epithelioid granulomas, giant cells and suppurative inflammation are observed. With these findings, granulomatosis and suppurative lymphadenitis should be considered within the differential diagnosis. Since the changes caused by tularemia in the lymph node biopsy histopathologically usually are in the form of granulomatous lymphadenitis having a course caseous necrosis, tularemia patients are often examined with regards to TB and an anti-TB treatment is started. This particular situation may cause some risks due to unnecessary anti-TB use, resistance and side effects. Six patients in Gün et al. (5) study who were clinically and serologically diagnosed with tularemia were evaluated with regards to cervical lymph node FNAB results and their cytomorphological characteristics were defined. In addition to the suppurative inflammation findings in all the six patients, caseous necrosis was also observed. The authors stated that TB and tularemia could not be histopathologically distinguished via cervical lymph node FNAB and also emphasized the importance of serology and clinical findings in making the correct diagnosis in such situations. Due to the non-necrotizing granulomatous lymphadenitis detection carried out in the first health center our patient visited, inti-TB treatment was commenced thinking that it might be TB lymphadenitis. We are of the opinion that to be able to make more careful differential diagnosis in the TB-endemic regions of our country, there will be greater chance of success in the treatment of tularemia-related lymphadenopathies just like in our case. Therefore, tularemia should always be considered in patients admitted for the complaints of lymphadenopathy.

In the treatment of tularemia, usually aminoglycosides (gentamycin and streptomycin), tetracyclines (tetracycline or doxycycline) and in meningitis cases, chloramphenicol and quinolon derivatives are used (8, 9). Before the antibiotics were started to be used, it was known that the improvement period of the disease was more than three months, total mortality rate was (7% (5-15%) and the mortality rate in serious cases (pneumonia and typhoidal form) was 33%. Today, the mortality rate has decreased to the level of 2% through antibiotic use (10-12). In the treatment of tularemia cases, aminoglycosides are the first choice. For this purpose, streptomycin (30-40 mg/kg/day, maximum 2 gr/day, im, 10 days) or gentamycin (5 mg/kg/day, iv or im, 10 days) are the recommended antibiotics. Although their use is not recommended for children except in compulsory situations, in the alternative treatment, ciprofloxacin (30 mg/kg/day, maximum 1200 mg/day) or doxycycline (4 mg/kg/day, maximum 200 mg/day) are possible to use. Depending on the body weight of the cases, antibiotics can be given parenterally or orally. The parenteral treatment given with ciprofloxacin and doxycycline may be switched to oral therapy when the patient's clinical situation improves. Streptomycin and gentamycin are the first agents preferred in children. In heavy (pneumonic forms, typhoidal form, meningitis, pericarditis etc.) and immunosuppressive cases, combination treatment can be given. For this purpose, aminoglycoside or doxycycline can be combined together with quinolons. In the tularemic meningitis, streptomycin treatment together with chloramphenicol (100 mg/kg/day, iv, 14-21 day) can be given (1).

The antibiotic treatment initiated in the early phase of the disease is more successful. If the treatment is delayed, the improvement period is prolonged. Despite the treatment with appropriate period and dose, lymph node suppuration and regressing lymph nodes may require long time (7). As in our case, in cases that are given a treatment in the second and third week, suppuration develops in the lymph node despite the treatment and the need for surgical intervention increases. In the study carried by Ayşe Willke upon the epidemic around Gölcük in 2004-2005, 188 patients were diagnosed with tularemia. It was concluded in the study that regression period of the complaints varied

between 5-180 days, and initiating the treatment later than seven days and the presence of abscessed lymph nodes delayed the treatment (13). In their study, Kaya et al. (14) diagnosed 27 patients with tularemia and reported that treatment of six patients were unsuccessful, 21 patients completely responded to the treatment; and that treatment period in non-responding patients was on average 26.5 day and in responding patients 17 days. In another study Ceylan et al. carried out with 13 patients, regarding the responses of the patients to the treatment they found that the median treatment period of the patients who were admitted seven days after the onset of the symptoms was 14 days, the median treatment period of those who were admitted after 14 days was 40 days (24-210), symptom and findings lasted for more than a month in six patients (65%), 8 patients were observed to need surgical excision and unsuccessful treatment was 61% (15). It is reported in the literature that non-subclinical cases may improve without treatment as well (1).

Conclusion

In conclusion, tularemia is a difficult disease to diagnose when it does not come to mind and its differential diagnosis should be made based on many clinical pathologic conditions. Therefore, in patients diagnosed with granulomatous lymphadenitis, in addition to TB, a prevalent disease in our country, tularemia that can be diagnosed with via a good medical history should always be borne in mind.

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