

Case Report of Systemic Tularemia in Cyprus

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Tularemia is a zoonotic infectious disease in the Northern Hemisphere, which is caused by gram-negative *Francisella tularensis* bacteria with four subtypes. In this article, a case of a 5-year-old girl with oculoglandular, oropharyngeal, and typhoid tularemia accompanied by lymph nodes in the abdomen has been presented. Amoxicillin-clavulanic acid treatment was first applied to the patient who had high fever, neck lymphadenopathy, and crypts in the tonsils. Intramuscular ceftriaxone therapy was started after the expected response could not be obtained. As a result, as there was no improvement in response to both the treatments in the clinical condition of the patient, and the patient was hospitalized. Physical examination revealed the presence of cervical and submandibular lymphadenopathy and left otitis media. Hepatosplenomegaly and bilateral periorbital edema developed on the day after admission to the hospital. The most frequent diseases in the age group of the patient that may cause the observed findings were tried to be excluded by laboratory and radiological data. Upon learning that the patient had contact with the suspected infected rabbit during treatment, *Francisella tularensis* antibody was ordered for differential diagnosis of tularemia. The test result was reported as 1:80 titre positive. The patient's treatment was changed to a combination of ciprofloxacin plus amikacin. A gradual improvement was observed, and a follow-up evaluation two weeks later revealed that the patient had recovered with no complication. This case is the first proven case feature and is worthy of showing the importance of getting detailed anamnesis.

Keywords: Tularemia, *francisella tularensis*, lymphadenopathy

INTRODUCTION

Tularemia caused by *Francisella tularensis* is transmitted by a direct contact of animals with humans through vectors, infectious aerosols, food, or water. The incubation period is 3–5 days on an average, which can last up to 21 days (1). The disease can be observed in different clinical manifestations according to the bacteria's virulence, entering area, and immune status of the person (2). There are six clinical forms of the disease: ulceroglandular, gastrointestinal, oculoglandular, oropharyngeal, typhoid, and pneumonic form. Patients may present general symptoms, such as fever and pain, and regional lymphadenopathies are often associated with the disease (3). Those living in rural areas, hunters, and veterinarians are considered as risk groups (4). In the Northern Hemisphere, where the disease is more common, ulceroglandular form caused by vectors such as ticks is seen at a high frequency. Oropharyngeal tularemia is the most common form of the disease is observed in Turkey. The agent is often contaminated with contaminated food and water. (1). It is the first case of tularemia reported in the Turkish Republic of Northern Cyprus (TRNC), where fever, pharyngitis, bilateral periorbital edema and hyperemia, mesenteric and cervical lymphadenopathy (LAP), hepatosplenomegaly and diarrhea are observed.

CASE PRESENTATION

A 5-year-old girl who lives in Nicosia city center was admitted to the emergency department with edema, erythema, endurance on the bilateral side, bilateral cervical and submandibular LAPs, fever up to 39°C, and crypt findings in the anterior tonsillar plaque (Figure 1). Amoxicillin-clavulanic acid treatment was started empirically on the patient who had pre-

viously applied to an external center 7 days ago. The patient's treatment was modified to be intravenous ceftriaxone after growth in the cervical lymph nodes and development of a deep neck infection table..Patient whose condition worsened despite treatment with ceftriaxone was referred to our hospital. During the examination of the patient in emergency department, left otitis media was detected in addition to epicrisis report. .It was reported that LAPs in the jugulodigastric chain on both sides not exceeding 18 mm were observed using neck ultrasonography (USG). Lesions were interpreted as reactive LAP. Abdominal USG revealed LAP in the vicinity of the pancreas. Biochemical parameters except amylase (324 U/L), C-reactive protein (11.13

mg/dL), antistreptolysin O (204 IU/mL), and sedimentation (38 mm/h) levels were within the reference value range. Leukocyte (12880/ μ L), neutrophil (65%), lymphocyte (25%), monocyte (6%), eosinophil (3%), and basophil (1%) concentrations were reported in the complete blood count and peripheral smear. The postero-anterior chest X-ray results, complete urine analysis, and throat culture studies were normal. The detection of BO I:320 titer positivity in the Salmonella group agglutination test suggests that there may be a Salmonella infection. Metronidazole was also added to the treatment because of watery, mucous defecation and leukocyte infiltration observed on the stool microscopic examination. On the fourth day of antibiotic treatment, despite regression in fever, in the clinical findings, subclinical LAP enlargement and bilateral periorbital edema and hyperemia were observed (Figure 2). On the patient's control; increased leukocyte count (20,000/ μ L), LAP of the size 36x23 mm² in the pancreas neighborhood and hepatosplenomegaly was observed (Figure 3).There was no growth in blood culture and Salmonella-Shigella media. Suspicion of malignancy was ruled out by the absence of free fluid and pathologic findings in abdominal and thoracic tomography. Serological tests for Epstein Barr IgM profile, Bartonella henselae, cytomegalovirus, toxoplasma, and Wright and Weil-Felix tests were negative. The PPD measurement was 0 mm (no BCG vaccine). After the subfebrile fever began to rise again, ceftriaxone and metranidazole were stopped and the treatment was continued with meropenem. On the sixth day of the meropenem treatment, leukocyte count (13000/ μ L) and bilateral periorbital edema decreased in the patient whose general condition was good and fever was under control. The next day, there was again an increase in bilateral periorbital edema and hyperemia. The general condition was gradually deteriorated and an increase in the size of the lymph nodes in the cervical and abdominal regions was observed. The fever again became resistant, and diarrhea was re-added to the disease table. In view of the clinical deterioration, it was learned that the patient was contacted with a wild rabbit hunted by his father during the re-questioning of the family. Despite the fact



FIGURE 1. Bilateral periorbital edema and induration



FIGURE 2. Bilateral submandibular lymphadenopathy



FIGURE 3. Mesenteric lymphadenopathy observed in abdominal ultrasonography

that tularemia has not been reported in Cyprus until this day, it has been thought that the patient may also have tularemia. For this purpose, a sample for *F. tularensis* micro-agglutination test, which is not performed in our country, was sent to a reference laboratory in the United States of America. Upon learning that the test would be reported in two weeks, the treatment was changed to ciprofloxacin plus amikacin. On the second day of the treatment, bilateral periorbital edema and hyperemia were reduced and cervical LAPs were stretched to 1.5 cm in size. On the fourth day of the treatment, fever, bilateral periorbital edema, and hyperemia were not observed, and clinical healing was seen. The treatment was continued for 10 days and the patient was later discharged. Meanwhile, the result of the *F. tularensis* antibody test was reported as 1:80 titer positive. On the fourteenth day of the treatment, the patient came for the control examination. There were no pathological findings. In cervical and abdominal USG examinations, no LAP and hepatosplenomegaly were observed. Informed consent was obtained from the patient's parents.

DISCUSSION

Tularemia shows different symptoms depending on the agent's entry location and the host's immune system (4).

People who are living in endemic regions and dealing with hunting and other natural sports who are showing the symptoms such as fever, pharyngitis, and LAP, should be detailed questioned in terms of tularemia (1). Since 2005, tularemia has been declared a mandatory disease by the Ministry of Health of the Republic of Turkey. The incidence of tularemia cases has been increasing in Turkey since 2009. The majority of cases are seasonally distributed between December and March (2). The majority of cases observed in Turkey are oropharyngeal tularemia cases (1). In the literature, it has been reported that preauricular, submandibular and anterior cervical LAPs are usually accompanied by other findings in tularemia cases (3).

F. tularensis is susceptible to antibiotics such as fluoroquinolones, aminoglycosides, and tetracycline. The treatment protocol should be planned for at least 10 days for fluoroquinolones and aminoglycosides and not less for 15 days for tetracycline and its derivatives (5).

Sarcoidosis, tuberculosis, cat scratch disease, brucellosis, leprosy, and leishmaniasis should be investigated in the differential diagnosis (3, 6). Considering the fact that the patient is 5 years old, these diseases were excluded in the differential diagnosis, mainly because sarcoidosis is usually seen in older ages and leprosy has the average incubation period for 5 years (7). The negativity of the *B. henselae* IgM and IgG by ELISA tests and the Wright serological agglutination tests have excluded the suspicion of cat scratch disease and brucellosis. The incidence of tuberculosis in TRNC is very low, so BCG vaccination is not routinely given. The applied PPD test was 0 mm. Although there are cases of cutaneous leishmaniasis in our country, there is only one case of Kala Azar that has been re-

ported to this day (8). Leishmaniasis was also excluded from the differential diagnosis because of the absence of skin lesions in our patient and the negative appearance of leishmania visceral antibody test. The familial Mediterranean fever, which has a high incidence in the Mediterranean region, has been ruled out since the fibrinogen level is within the reference value range.

Small mammals such as rabbits, mice, squirrels are considered natural reservoirs for *F. tularensis* (2). For this reason, in those who have a contact story with an animal that is suspected of being infected, the possibility of tularemia should be considered in the presence of long-term fever, throat and / or eye infection findings that do not respond to antibiotics.

The duration of antibody response in Tularemia varies between 1 and 21 days (1). The positive 1:80 titer test result is thought to be related with early sample collection time. LAP findings accompanying with diarrhea and throat and eye infection findings in the patient suggested a systemic tularemia infection together with oculoglandular, oropharyngeal, and typhoid forms. The tularemia confirmation test was not repeated because the patient's family did not want to give blood sample again.

CONCLUSION

According to a report published in 2016 by the European Center for Disease Prevention and Control Center, between 2010-2014 it has not detected any cases in Cyprus (9). Our patient is the first case diagnosed and reported in TRNC. For this reason, we believe that it is important to consider tularemia in the differential diagnosis for early detection cases with similar complaints.

Informed Consent: Written informed consent was obtained from patient's parents who participated in this study.

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