Abstract

**Background:** Francisella tularensis is a gram-negative zoonotic pathogen primarily of animals and occasionally of humans. The disease is now recognized as tularemia in most parts of the world, but it has been called rabbit fever, deer-fly fever, and market men’s disease in the United States; wild hare disease (yato-byo) and Ohara’s disease in Japan; and water-rat trappers’ disease in Russia. Tularemia continues to be responsible for significant morbidity and mortality, despite the availability of numerous antibiotics active against the organism. The first cases of tularemia in Kosovo are reported in the southwestern part of Kosovo, in the region of Gjakova in April 2000 in the village of Brovina - 22 patients who were infected through contaminated well water. In the meantime disease is spread in villages of Skivjan, Korenica, Batusha and later throughout Kosovo.

**Aim:** The aim of this study is presentation of characteristics of Tularemia in Kosovo in 2010 and analyzes of the epidemiological, clinical and treatment features of Tularemia in Kosovo.

**Methods:** We analyzed 53 cases of tularemia (from 320 patients with tularemia in Kosovo in 2010) that were from 12 municipalities of Kosovo. The largest number of patients were from Municipality of Vushtrria (11 patients) and municipality of Skenderaj (9 patients). All these cases were from rural areas; this confirms that social and epidemiological conditions are very important for appearance of this disease. We have analyzed the data from their medical histories, which includes their medical anamnesis, clinical examination, laboratory tests and their treatment.

**Results:** The mean age of patients was 22 years, 13 patients were children under the age of 10 years. Patients were hospitalized an average of 14.7 days, while incubation time of the disease was an averaging of 28 days. Social and epidemiologic conditions were important factors in the appearance of the disease; 29 patients were water supplied only from
wells. All patients were from rural areas. Clinical manifestations were temperature, neck pain, neck and axillary lymphadenopathy, and apathy. Clinically, glandular form has dominated.

From laboratory tests, 51 of patients had high erythrocyte sedimentation rate, 13 cases had a slight anemia, and 34 patients had leukocytosis. Other laboratory tests were in normal values. Agglutination test in all cases was positive. All cases were treated with antibiotics; 31 patient were treated with gentamicin, 8 patients were treated with streptomycin and 14 patient were treated with other antibiotic. Incision and drainage of the gland as adjuvant therapy was applied in 27 patient.

Conclusions: In this late decade in our country, tularemia continues to be a disease that represents a healthcare problem. Glandular forms of tularemia dominate in Kosovo. Treatment with gentamicin has had good effects. Incision and drainage of the inflamed glands has shown to be a good method in accelerating the recovery of patient. Prophylaxis has to be applied for prevention of the disease.

Key words: tularemia, temperature, lymphadenopathy, gentamicin

1. Introduction

Tularemia is an acute infectious disease, which makes place in group of zoonoses, it is caused by bacterium Francisella Tularensis. Tularemia is known also as “rabbits fever” and “deer fly fever”.

Tularemia was described for the first time as clinical entity in Japan in 1837. Tularemia is named by the region of Tulare in California (USA) in 1911. The cause of disease is isolated by Dr. Edward Francis in 1916, by who also gets the name.

First cases of Tularemia in Kosovo occurred in 2000, after the end of the war. In 2000, an epidemic of Tularemia in Kosovo resulted with around 600 people infected. First cases of Tularemia in Kosovo were reported on April of 2000 in Brovina village-district of Gjakova and than in other parts of Kosovo: Peja, Decan, Klina, etc. In 2010 in Kosovo were reported 320 cases of Tularemia, of which 53 patient were hospitalized for treatment in Clinic for Infectious Disease in Pristina.

1 Dodaj-Ejupi T. Epidemia e Tularemisë në Kosovë (punim magjistrature), Prishtinë, 2007.
According to the WHO, after 2000, Kosovo belongs to the group of countries with endemic Tularemia.4

The aim of the study: Presentation of the cases with tularemia in Kosovo, presentation of the cases with tularemia in Kosovo, and the analyses of the epidemiological, clinical and treatment features of Tularemia in Kosovo during the period January – December 2010.

2. Methods

We analyzed 53 patient treated for Tularemia in Clinic for Infectious Disease in Pristina, who were from 12 different municipalities of Kosovo (of 36 municipalities that has Kosovo) most of which are entitled as endemic regions in Kosovo. All these cases were from rural areas. Data are taken from medical histories and have included anamnesis, clinical examination, laboratory tests and treatment.

3. Results

3.1. Epidemiological characteristics: All patients were from 12 municipalities some of which are endemic areas for Tularemia (Vushtria with 11 cases, Skenderaj with 9 cases) and some municipalities that in 2000 had have less cases of Tularemia (Bushë Kosova in 2010 had 5 cases, Ferizaj 5 cases, Lipjan 5 cases, Shtimja 5 cases). All the cases have been from rural areas. From 53 cases with tularemia, 29 of them were supplied only with water from wells, 19 cases were supplied with water from water supply system and 5 cases were supplied from both sources – wells and water supply system.

From 53 analyzed patients, female gender has dominated, 29 patients were females and 24 were males. Patients were young-to-middle age, average age was 22 years. 29 patient or 54.7% of patients were over the age of 18 year and 24 or 45.3% of patient were young patients, under 18 year.

Table 1. Gender/Age ratio of patients.

<table>
<thead>
<tr>
<th>Gender/ Age</th>
<th>0-18 years</th>
<th>Over 18 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>10</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>F</td>
<td>14</td>
<td>15</td>
<td>29</td>
</tr>
</tbody>
</table>

4 WHO Guidelines on Tularaemia,2007,

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3.2. Clinical forms of disease: All patients had more than one clinical form with domination of glandular form. None of the patients had intestinal manifestation of the disease.

Glandular form: was most common form of manifestation of the disease. From 53 cases treated in Clinic for Infectious Disease 52 cases had glandular form of the disease. This shows that in Kosovo dominates the glandular form of disease which in America is presented in 3 to 20% of cases5,6.

Ulceroglandular form: From 53 cases only 3 cases had ulceroglandular form of disease.

Oropharyngeal form: From 53 patients treated in our clinic only 13 cases have manifested oropharyngeal form of the disease. This form has been manifested in 25% of cases.

Oculoglandular form of disease had only one patient.

Pulmonic form: From 53 cases 11 patients or 21% have had also pulmonary manifestation of the disease.

Typhoidal form was manifested in 3 patients or 6% of cases.

In clinical presentation have dominated high temperature and throat pain in all the patients (53 cases or 100%), swelling of lymph nodes in 52 patients (98%), malaise and fatigue 50 patients (94%), chills 41 patients (77%), sweating 31 patients (58%) and 27 patients or 51% of cases had indurations of lymph nodes. All the patients had two or more clinical signs7,8.

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### Table 2. Clinical manifestations

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Gender</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>M</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>High temperature</td>
<td></td>
<td>29</td>
<td>100</td>
<td>24</td>
<td>100.0</td>
</tr>
<tr>
<td>Throat pain</td>
<td></td>
<td>9</td>
<td>100</td>
<td>24</td>
<td>100.0</td>
</tr>
<tr>
<td>Malaise and fatigue</td>
<td></td>
<td>9</td>
<td>100.0</td>
<td>21</td>
<td>87.5</td>
</tr>
<tr>
<td>Swelling of lymph nodes of the neck</td>
<td></td>
<td>7</td>
<td>93.1</td>
<td>24</td>
<td>100.0</td>
</tr>
<tr>
<td>Other lymph nodes swelling</td>
<td></td>
<td>1</td>
<td>3.4</td>
<td>2</td>
<td>8.3</td>
</tr>
<tr>
<td>Chills</td>
<td></td>
<td>7</td>
<td>87.5</td>
<td>1</td>
<td>50.0</td>
</tr>
<tr>
<td>Sweating</td>
<td></td>
<td>14</td>
<td>48.2</td>
<td>17</td>
<td>70.8</td>
</tr>
</tbody>
</table>

**Figure 1.** Neck lymph node after incision.  
**Figure 2.** Indurated lymph node.  
**Figure 3.** Chest X-ray with pulmonic manifestation of Tularemia.  
**Figure 4.** Chest X-ray with pulmonic manifestation of Tularemia.
4. Diagnosis

Erythrocyte sedimentation rate was high in 51 patients from 53 analyzed in total. Hemogram had no significant differences, slight anemia have been noted in 13 patients. Leukocytosis had 34 patients. In all cases the agglutination test was positive.

The main diagnosing method was serologic method. Agglutination test was positive as early as in first week in one patient while in all patients after the second week. In three cases the first serologic test was negative, while in three cases in the first serologic test the titer of agglutination was 1:80, in all other cases the titer of agglutination was 1:320. In the second test after the fourth week in only one case the agglutination test was negative, while in 52 cases the test was positive with agglutination titer 1:320.

Table 3. Agglutination titer level according to weeks.

<table>
<thead>
<tr>
<th>Titer level</th>
<th>Weeks</th>
<th>Neg.</th>
<th>1:80</th>
<th>1:160</th>
<th>1:320</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>I-II</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>After the IVth week</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>52</td>
<td>53</td>
<td></td>
</tr>
</tbody>
</table>

Neck ultrasound is taken in 14 patients. (Figure 5 and 6)

Figure 5. US of a lymph node where is noted presence of fluid. 

Figure 6. US of a lymph node where is noted peripheral vascularisation and missing of vascularisation in center.

5. Treatment

All the cases were treated with antibiotics; the primer antibiotic that was used in treatment of tularemia was Gentamicin which was used as initial therapy in 31 patients or 58.4% of cases, while Streptomycin was used as initial therapy in 8 patient or 15% of cases. In 29 patients or 54.7% of cases therapy was repeated; this shows that there was poor manage of treatment of patients with tularemia. Incision and drainage was applied in 27 patients or
50.9%, method for which in epidemic of 2000 WHO recommended not to apply because of risk of infection of the wound and high infectivity of tularemia.

Table 4. Treatment of patients with tularemia.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Gentamicin</th>
<th>Streptomycin</th>
<th>Other Antibiotic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with base therapy</td>
<td>31</td>
<td>8</td>
<td>14</td>
<td>53</td>
</tr>
<tr>
<td>No. of patients with repeated therapy</td>
<td>16</td>
<td>13</td>
<td>0</td>
<td>29</td>
</tr>
</tbody>
</table>

6. Discussion

Tularemia occurs more frequently in Scandinavian countries, America, Russia and Japan, but recent cases of tularemia have also been reported from countries like Turkey, Kosovo and Serbia, which implies that tularemia is a disease that has spread throughout the world.

Tularemia is an epidemic disease in Kosovo, which occurs in sporadic forms over the years. First cases of tularemia in Kosovo are presented after 1999, after the war in Kosovo.

Since 1999/2000 when we had the first epidemic of tularemia in Kosovo, new cases of tularemia has been consistently reported with a high number of patients in 2010.

The most frequent clinical form of tularemia in Kosovo is the glandular form, which is presented in almost all cases of tularemia in Kosovo, while in America this form is presented in 3-20% of the cases.

The diagnosis of tularemia is based on epidemiological data, clinical features, and laboratory, microbiological and serological tests.

The 29 cases in this study were supplied with drinking water from the well and are not connected to the sewage system. This suggests the possibility that the most common source of infection is drinking water from wells. In 24 out of 53 analyzed cases or 45.2% diagnosis was set too late, one month after the lymph node swelling. This shows that early detection is not an easy task and can be confused with other causes of lymphadenopathy.

In clinical terms, we had general manifestations of infection such as: temperature and pain in all patients (100%), swelling of the lymph nodes (98.1%), weakness (94.3%), fever (80%), and sweating (58.4%).

From laboratory tests we had a slight increase of erythrocyte sedimentation rate (51 patients) and a slight anemia in 13 patients, slight leukocytosis 34 patients, indicating developments of tularemia in the ordinary course of illness.

The agglutination test after the second week was positive in 50 patients; in 3 patients the test was negative. In threecases levels of the agglutination titer was
1:80, while in 47 cases agglutination titer was 1:320. The second test of agglutination after the fourth week was positive in 52 patients (1:320), while one patient was negative.

In 52 patients the diagnosis of disease is made by the agglutination test and in one case the diagnosis is established by histopathological examination of specimen taken from a lymph node.

In 31 cases the treatment is done with gentamicin and in 8 cases with streptomycin. This treatment is also used in many other studies. In 29 cases we had relapse of disease, in 16 cases after therapy with genatmicin and in 13 cases after therapy with streptomycin. Mild forms of tularemia can be treated with doxycyclin, erythromycin or bactrim.

Apart from drug treatment in 27 cases incision and drainage of swelled lymph node is made and this has affected in more rapid removal of swelling of lymph node. This form has been successful in our cases, although not recommended by WHO.
7. Conclusions
Tularemia continues to be one of the health problems of Kosovo. There are still difficulties in defining the epidemiological mechanism of the disease.

Drinking water supplied from wells is one of the socio-epidemiological problems that contribute to the appearance of the disease.

The disease appears in rural areas.

In Kosovo, glandular form of tularemia continues to dominate.

There are still problems in clinical diagnosis because doctors do not think on tularemia in early lymph node swelling.

Treatment protocols for tularemia should be harmonized; response to treatment with gentamicin is good.

Apart from drug treatment in 27 cases incision and drainage of swelled lymph node is made and this has affected in more rapid removal of swelling of lymph node. This form has been successful in our cases, although not recommended by WHO.

Cooperation between Clinic for Infectious Disease and other institutions should deepen in order of early detection of tularemia.
8. References