A tularemia outbreak in an extended family in Tokat Province, Turkey: observing the attack rate of tularemia

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Summary

Objective: We report the first tularemia epidemic occurring in Tokat Province, located in the Middle Black Sea Region of Turkey, and some features of the cases. This epidemic has allowed the calculation of the attack rate of this disease because of its appearance in a single large family.

Methods: The clinical and laboratory features of patients were examined. For serological diagnosis, microagglutination assays were done on serum samples from patients and other members of the family.

Results: Seven members of the family developed overt clinical disease (one ulceroglandular, six oropharyngeal). Three patients had conjunctivitis in addition to oropharyngeal involvement. All patients had a microagglutination titer above 1/160. As eight out of 16 members of the extended family were found to be positive for tularemia serology, the attack rate was calculated to be 50%.

Conclusions: Tularemia is highly infectious and different clinical forms can occur in a single epidemic.

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Introduction

Tularemia, a disease caused by the bacterium Francisella tularensis, is characterized by fever and lymphadenopathy. Tularemia is a zoonosis in which the sources of infection are primarily small animals such as mice, squirrels, voles, hares, and beavers. Ticks and flies are vectors that may play an important role in transmission of the bacteria to humans.1,2 While epidemics related to tick bites are frequently seen in the summer season, epidemics seen in the winter season are generally related to contact with animals or the use of contaminated water. F. tularensis comprises four subspecies, two of which are clinically and epidemiologically important. F. tularensis subsp. tularensis is generally seen in North America, is the more virulent, and is related to tick bites. Strains of F. tularensis subsp. holarctica cause a milder disease; epidemics are related to contact with infected animals or contaminated water and are primarily seen in Euroasia.2–4
Tularemia comprises six different clinical forms. Although the ulceroglandular form is most frequently reported in the international literature, the form most frequently seen in Turkey is the oropharyngeal type. The first tularemia epidemic in Turkey was reported in 1936, and since then other epidemics have been seen, especially in the northwestern part of the country. Here we present the first tularemia epidemic occurring in Tokat Province, located in the middle Black Sea region of Turkey, and some features of the cases. This epidemic has allowed the calculation of the attack rate of the disease because of its appearance in a single large family.

Patients and methods

Seven cases, all members of the same extended family, were admitted to our infectious diseases outpatient clinic in December 2005. All cases had experienced a febrile illness 20–25 days before admission to our clinic. None of the patients had fever on admission. Complete blood counts, erythrocyte sedimentation rates (ESR), and C-reactive protein (CRP) levels were measured. A diagnosis of tularemia was suspected due to clinical findings; for specific diagnosis, sera of the patients were sent to Uludag University Microbiology Laboratory for microagglutination assay. The antigen used in the serological tests was prepared from an F. tularensis strain. Antibody titers of 1/160 and above were accepted to be significant for diagnosis. Two weeks after the definite diagnosis of tularemia, a visit was made to the patients’ house in the village. Serum samples were obtained from nine healthy members of the family and were sent to the same laboratory for tularemia microagglutination assay. We received an informed consent from all study participants. In addition, a proxy consent was taken for the mentally retarded case.

Results

Of seven patients admitted to our clinic, five had cervical adenopathy and one patient had adenopathy with location other than cervical. The first case, a 33-year-old woman, was the only one who did not have cervical adenopathy (case 1, Table 1). One month before admission to our clinic she learned that he had experienced flu-like symptoms during the same period, suggesting the oropharyngeal form. Five patients developed cervical swelling or preauricular LAP, but one patient had no lymphadenopathy (Table 1). All patients had been previously misdiagnosed with bacterial pharyngitis by specialists in otorhinolaryngology or general practitioners and had been treated with beta-lactams or macrolides without any benefit. Fever lasted for 1–2 weeks in these patients. Three patients had symptoms of conjunctivitis during the illness and one of them was given topical antimicrobial treatment. Conjunctivitis improved in all patients without any complications. All patients were found to be positive for tularemia serology by microagglutination assay (Table 1).

During the visit made to the patients’ house in the village, we observed that the family had two water sources, one from the village water supply and the other from a natural spring. The exit site of the spring was closed and water was carried to the house via pipes. It appeared that there was no contamination risk with dirty water or wild animals. However, they reported that there were a lot of mice around or in the house and that food may have become contaminated with their secretions, as they stocked grains and some other foods in the house. They had had no contact with dead animals. There were no other tularemia patients in the village. Examination of health records also revealed that there had been no other cases of tularemia in this region up until this time, and that these patients were the first cases reported from Tokat Province.

Among nine healthy members of the family, only one had a titer greater than 1/160 by microagglutination assay. The others were found to be seronegative. The person with positive serology was a 30-year-old mentally retarded man (case 8, Table 1). He had no symptoms at the time of visit, but we learned that he had experienced flu-like symptoms during the same period.

Aminoglycoside monotherapy (streptomycin 1 × 1 g for adults and gentamicin 5 mg/kg/day for children) was given to four patients. Streptomycin plus doxycycline was given to

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Gender</th>
<th>Lymphadenopathy</th>
<th>Clinical form</th>
<th>Conjunctivitis</th>
<th>Microagglutination titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>F</td>
<td>Axillar, epitrochlear</td>
<td>Ulceroglandular</td>
<td>No</td>
<td>1/640</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>M</td>
<td>Cervical</td>
<td>Oropharyngeal</td>
<td>No</td>
<td>1/640</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>F</td>
<td>Cervical</td>
<td>Oropharyngeal</td>
<td>No</td>
<td>1/2560</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>M</td>
<td>Submandibular, preauricular</td>
<td>Oropharyngeal</td>
<td>Yes</td>
<td>1/1280</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>F</td>
<td>Cervical</td>
<td>Oropharyngeal</td>
<td>Yes</td>
<td>1/1280</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>M</td>
<td>Cervical</td>
<td>Oropharyngeal</td>
<td>No</td>
<td>1/1280</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>M</td>
<td>No</td>
<td>Oropharyngeal</td>
<td>Yes</td>
<td>1/320</td>
</tr>
<tr>
<td>8a</td>
<td>30</td>
<td>M</td>
<td>No</td>
<td>Oropharyngeal</td>
<td>No</td>
<td>1/320</td>
</tr>
</tbody>
</table>

*This case had a history of fever and sore throat, but was not admitted to our clinic; a microagglutination test was carried out on a serum sample obtained from this patient during a house visit.*
one patient because of a large cervical lymphadenopathy. Two patients started treatment with doxycycline because one of them was old and one had a previous history of illness without lymphadenopathy at admission, but had a high ESR and high CRP level. Some of the laboratory findings and the treatments given to the patients are shown in Table 2.

A surgical approach was required for two patients. These patients developed fluctuation of the adenopathy after they had completed the 14 days of medical treatment (Table 2). The preauricular adenopathy in the 4-year-old patient was aspirated with a needle and the cervical adenopathy in the 33-year-old woman was drained through an incision.

Although a slight regression of adenopathies was observed at the end of treatment, a significant regression was observed at two weeks after completion of treatment and it was shown that adenopathies almost fully regressed one month later (after the completion of treatment). A failure of doxycycline treatment was considered in one patient, as he had persistent constitutional syndrome with elevated markers of inflammation. A further course of antibiotic treatment with ciprofloxacin 500 mg bid for 14 days was given to the patient, which was successful (Table 2).

Eight of 16 members of the family were found to be positive for tularemia by microagglutination assay. Hence the attack rate of tularemia was calculated to be 50%.

**Discussion**

Tularemia is transmitted in several different ways to humans. Tick or fly bites are the most frequent means of transmission. The bacteria can survive for long periods in water sources or in animal carcasses. The oropharyngeal form of the disease characterized by pharyngitis and lymphadenopathy can occur as a result of ingestion of contaminated water or food. When bacteria are inoculated into conjunctiva, the ocular form of the disease occurs. Bacteria may also enter into the respiratory system and lead to pneumonic tularemia. Oropharyngeal tularemia in particular has increasingly been reported from different parts of Europe. Although in these reports almost all cases have had one form of the disease, there have been a few reports in which the oropharyngeal and ulceroglandular forms have been seen in the same epidemic. In our epidemic one patient had the ulceroglandular form, but the others had the oropharyngeal form. Reinjtes et al. investigated a tularemia outbreak that occurred in Kosovo in the early postwar period, 1999–2000. They reported that all cases were in the oropharyngeal form and that the possible source of infection was contaminated water or food. Helvacı et al. investigated 205 cases of tularemia from small epidemics or occurring sporadically between 1988 and 1998 in Turkey. They reported that the oropharyngeal disease was the most frequent clinical form (83%) and that epidemics were related to contaminated water. Four of 205 patients had the ulceroglandular or glandular disease. In recent years, reports of tularemia epidemics from the northwestern part of Turkey have shown that almost all cases developed the oropharyngeal type. In a recent report from Suluova, Turkey, unlike in the other epidemics, the glandular form was found to be the most common (60.4%), followed by the ulceroglandular form; only 4.7% of cases had the oropharyngeal form.

It seems most likely that the source of the present epidemic was contaminated food or water, because all patients except one developed the oropharyngeal disease. The patient with ulceroglandular disease (case 1) may have got the bacteria through the skin via handling or touching the contaminated food or water. Because all cases occurred within a few days, human-to-human transmission was considered not to have taken place. Also, they had no history of risk factors such as tick bite or contact with dead animals. Another interesting feature of the present epidemic was that three out of seven patients who had the oropharyngeal disease developed conjunctivitis in addition to fever, sore throat, and cervical lymphadenopathy. In the ocular form of tularemia, infection occurs as a result of the transfer of bacteria on the fingertips or from contaminated splashes and aerosols to the conjunctiva. The finding of conjunctivitis occurring in the course of oropharyngeal disease in the present epidemic may have been as a result of autoinfection, through transfer of the bacteria in oral secretions by means of the patients’ own hands. Thompson et al. reported a case of ocular tularemia in which the bacteria were transmitted via contact with a wild animal. Celebi et al. reported that four patients had findings of ocular tularemia in the oropharyngeal tularemia epidemic that affected 61 individuals in the northwest of Turkey. Two other waterborne tularemia outbreaks have occurred in Duzce, Turkey in the years 2000 and 2005. The oropharyngeal form was the most commonly seen type in both outbreaks, whereas three of the total of 11 patients affected in the 2005 outbreak had the ocular form. In 2004, Leblebicioglu et al. investigated a tularemia epidemic seen in Suluova, Amasya Province, which neighbors Tokat Province. They observed the concomitance of

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**Table 2** Laboratory findings at presentation and treatments applied

<table>
<thead>
<tr>
<th>Case No.</th>
<th>ESR (mm/h)</th>
<th>Leukocyte count ($\times 10^9$/l)</th>
<th>CRP (mg/l)</th>
<th>Treatment</th>
<th>Surgery</th>
<th>Treatment failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>8.470</td>
<td>10.2</td>
<td>Strep</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>9.690</td>
<td>16</td>
<td>Dox + Strep</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>88</td>
<td>9.210</td>
<td>27.6</td>
<td>Strep</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>13.540</td>
<td>7.96</td>
<td>Genta</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>12.890</td>
<td>&lt;5</td>
<td>Genta</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>8.470</td>
<td>41.5</td>
<td>Dox</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>12.060</td>
<td>8.91</td>
<td>Dox</td>
<td>–</td>
<td>No</td>
</tr>
</tbody>
</table>

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Genta, gentamicin; Strep, streptomycin; Dox, doxycycline.

a This patient underwent a diagnostic adenectomy.

b After treatment failure with doxycycline, ciprofloxacin was given to this patient.
conjunctivitis with the glandular form in five cases and suggested that the infectious agent spreads to the eye by rubbing or scratching following contact with infected animals or water.

Sixteen people were living in the same house, so all were exposed to the same risk factors. When serologic tests were applied to the sera from persons who did not show any symptoms but who had been exposed to the same risk factors, it was found that only one person had high titers of tularemia (titer of 1/320). Thus, eight patients were affected by this epidemic and the attack rate was calculated to be 50% (8/16).

The infective dose of the tularemia agent in humans is extremely low—10 bacteria when injected subcutaneously and 25 when given in an aerosol form. Although it is known to be an extremely contagious pathogen, we found no report on the attack rate of tularemia in the English language medical literature. In the present epidemic the source of infection was thought to be contaminated food or water and the attack rate was 50%. Because brucellae and *Yersinia pestis* are similar pathogens to the tularemia agent, we can compare the attack rate of tularemia with the attack rate to Brucella infections. Hence, the present tularemia epidemic shows a similar attack rate to Brucella infections.

In conclusion, these cases clearly show that different clinical forms of tularemia can occur despite originating from the same infection source. This may be explained by the high infectivity of the tularemia agent and the different ways in which the bacteria may enter the host body.

**Conflict of interest:** No conflict of interest to declare.

**References**


