

Unusual case of neck lymphadenopathy – oculoglandular form of tularemia

Nietypowy przypadek pacjentki z limfadenopatią szyjną – postać oczno-węzłowa tularemii

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ABSTRACT:

Tularemia is anthroponosis caused by Bacteria *Francisella tularensis* a gram negative, non-motile aerobic bacillus [5, 8]. The bacteria is transmitted mostly by rabbits, hares, rodents and arthropods. The pathogen penetrates into an organism via damaged skin, conjunctiva or mucosa- either through inhalation or ingestion. The clinical manifestations depend on the route of acquisition. Six forms of the disease can be distinguished: ulceroglandular or glandular, oculoglandular, oropharyngeal, respiratory, typhoidal, and intestinal [11]. We present a case report of the rarest oculoglandular form of tularemia. The patient was admitted to the hospital with right pre-auricular swelling, right sided neck lymphadenopathy, conjunctivitis and a nodule of the right eyelid. After excluding more common differential diagnoses, an ELISA test was performed and *Francisella tularensis* antibodies were identified. Patient administered proper antibiotic therapy. Tularemia is a rarely occurring disease in Poland and is nearly never taken into consideration by otorhinologists when diagnosing patients with neck lymphadenopathy. In clinical practice, otorhinologists should always consider this infectious zoonosis, especially the oculoglandular and oropharyngeal forms, as delayed diagnosis and treatment may cause serious health consequences in patients. In the future new drug research should be conducted because of the adverse effect of widely used medications specially for children and pregnant woman.

KEYWORDS:

neck lymphadenopathy, tularemia, *Francisella tularensis*, otorhinology

STRESZCZENIE:

Tularemia jest antropozoonozą wywołaną przez wewnątrzkomórkową gram ujemną bakterię tlenową *Francisella tularensis*, bardzo rzadko występującą w Polsce [5, 8]. Najczęściej przenoszona jest przez króliki, zające oraz inne gryzonie, a także stawonogi. Patogen wnika do organizmu przez uszkodzoną skórę, spojówkę lub błonę śluzową – drogą wziewną lub pokarmową. W zależności od drogi wnikięcia możemy wyróżnić 6 postaci tularemii: wrzodziejąco-węzłową, oczno-węzłową, ustno-gardłową, płucną, durową oraz jelitową. Przedstawiamy przypadek pacjentki, u której wystąpiła najrzadsza forma tularemii – postać oczno-węzłowa [11]. Pacjentka zgłosiła się na Oddział Otorinolaryngologii jednego ze szpitali na podkarpaciu z powodu obrzęku w okolicy przedusznej prawej, powiększenia węzłów chłonnych szyi po stronie prawej oraz guzka powieki górnej i zaczerwienienia spojówki oka prawego. Po wykluczeniu najbardziej prawdopodobnych przyczyn powodujących limfadenopatię szyjną przeprowadzono badania ELISA, w którym zostały wykryte przeciwciała *Francisella tularensis*. Po potwierdzeniu choroby pacjentka otrzymała leczenie celowane. Na oddziałach otorinolaryngologicznych praktycznie nie jest brana pod uwagę w diagnozowaniu chorych z towarzyszącą limfadenopatią szyjną. W praktyce laryngologicznej powinniśmy jednak pamiętać o tej chorobie zakaźnej, a szczególnie o jej postaci oczno-węzłowej i ustno-gardłowej, ponieważ opóźnienie diagnozy i leczenia może prowadzić do poważnych konsekwencji zdrowotnych.

SŁOWA KLUCZOWE: limfadenopatia szyjna, tularemia, *Francisella tularensis*, otorinolaryngologia

BACKGROUND

Tularemia is an anthroponozoonosis caused by *Francisella tularensis*, a gram negative, non-motile aerobic bacillus, which was first described in 1911 by doctor Edward Francis in Tulare, California as a pathogen occurring in squirrels [5, 8]. *Francisella* as well as anthrax and *Clostridium botulinum* is figured as a type A bioterrorist agent because of high virulence, ease of spread and high pathogenicity [10, 6]. The bacterium is frequently transmitted by hares, rabbits, rodents and arthropods through direct contact with animal tissues, fluids or via tick borne vectors. The pathogen penetrates into an organism by way of damaged skin, conjunctiva or mucosa, either through inhalation or ingestion. A few days post exposure, high fevers, myalgias and joint pains occur. Initially, a papule erupts at the exposure site, followed by ulceration with local oedema and regional lymph node enlargement. The clinical symptoms of tularemia may be different and depend on the route of acquisition. The ulceroglandular form is the most common, which leads to purulent lymph nodes. The rarest form of the disease is oculoglandular which occurs in 1% infected people. Tularemia spreads mostly in the northern hemisphere more commonly during the summertime [11]. This zoonosis appears infrequently in Poland which is why it is not routinely taken under consideration when forming differential diagnoses for patient with lymphadenopathies.

CASE REPORT

A 41 year old female farmer, with no history of any chronic illness, was admitted to the ENT department for right pre-auricular swelling, right side neck lymphadenopathy, conjunctivitis and a nodule of the right eyelid. On review of systems, she additionally noted fevers, malaise, and myalgias for a few days prior to presenting to the hospital. She was treated with Clindamycin orally by her general practitioner. In the hospital, blood analysis found an elevated C-reactive protein level and leucocytosis with monocytosis. The patient claimed that she was bitten by a tick one month before symptoms began. The testing for mononucleosis, toxoplasmosis, cytomegaloviral disease, and Lyme disease was negative. Despite antibiotic therapy (Cefuroxime) there was no improvement in the woman's condition. Her facial oedema [WU3] expanded and she continued to be febrile. A dentist, dermatologist and ophthalmologist were consulted. Erysipelas was suspected and antibiotic therapy was broadened to Ceftazidime, Vancomycin, and Metronidazole. Blood tests did not confirm any autoimmune diseases. Imaging (CT scans, magnetic resonance imaging and ultrasonography) showed soft tissue infiltration with abscess and regional lymph node enlargement. The patient underwent incision and

drainage of the abscess under local anesthesia, and the purulent content was sent for bacteriological examination. Histopathological examination found granulomatous tissue with chronic inflammatory infiltration. Due to lack of clinical improvement with existing antibiotic treatment, Linezolid was administered to the patient. A pulmonologist and infectious disease specialist were consulted and she was transferred to the ENT Clinic at the Kliniczny Szpital Wojewódzki nr 1 Rzeszów, Poland [WU4]. During her hospitalization, infectious disease doctor was consulted [WU5]. The patient underwent an operation under general anesthesia and detailed tests were taken. The following diseases were excluded: cat scratch disease, tuberculosis and actinomycosis. Histopathological examination showed non-specific granulomatous [WU6] tissue. Upon further questioning, the patient recalled having been scratched by her rabbit while cleaning its cage a few days before the first symptoms occurred. Additionally one of the patient's cows had a miscarriage earlier that year. This information led us to think about zoonosis – tularemia and brucellosis. Blood ELISA tests were taken and *Francisella* antibodies were found. The tests were performed in laboratories in Warsaw and Lublin. Proper treatment was administered – Streptomycin and Doxycycline. Liver enzymes were monitored and hearing tests were performed. Finally, the patient's general condition began to improve and her localized symptoms slowly resolved. After a few weeks of inpatient treatment, the patient was discharged with recommendations to return for follow up at the outpatient ENT clinic. After one year of treatment, her antibody levels were significantly diminished; ultrasonography examination showed a few minimally enlarged cervical lymph nodes; and her hearing test was within normal range. She continues to be monitored in follow up by both otolaryngologist and infectious disease specialists.

DISCUSSION

Tularemia is an infectious disease of wild or domestic animals as well as humans. The most characteristic symptom as a response to a *Francisella tularensis* bacteria acquisition is regional lymphadenopathy. The most common reservoirs in the environment are rabbits, hares, squirrels, mice, rats and arthropods, within whom the bacteria multiply very intensely, allowing for further transmission to future generations of arthropods, who transmit the pathogens to their offspring. Other insect vectors of *Francisella* include flies, horseflies, mosquitoes, and to a lesser extent fleas, bugs, lice, and mites. Other animal hosts include larger mammals (foxes, coyotes, dogs, cats, cattle, sheep, pigs) as well as wild fowl [1]. People at highest risk of being exposed to this pathogen are breeders, farmers, hunters, vets and microbiologists.

Tularemia is transmitted by either direct contact with a sick

animal or through infected tissues or fluids or contaminated food, water, dust or aerosol. The bacteria can penetrate into an organism through the skin, conjunctiva, mucosal membrane of the oral or nasal cavity, respiratory or gastrointestinal tract. The incubation period lasts from 1 to 21 days (mean 3–5 days) and excretion into the blood occurs at 1–2 weeks [11]. The bacteria remain within the purulent lymph nodes for about 4 weeks [2]. Those who acquire *Francisella tularensis* maintain permanent immunity to the disease [1]. The clinical manifestations depend on the route of acquisition. Symptom onset is acute and resembles viral illness with fever up to 40°C (lasting 2–4 weeks), chills, headache, nausea, vomiting, and rash.

Six clinical forms of tularemia can be distinguished:

1. Glandular and ulceroglandular forms (95%) – Papules and pustules occur at the area of damaged skin., followed by development of inflammatory infiltration and ulceration with regional lymph node enlargement. Most times this leads to supuration.
2. Oculoglandular form (1%) – Dominant findings include eyelid edema or granulomas, unilateral conjunctivitis, photophobia, excessive lacrimation and lymphadenitis of preauricular, neck, submandibular nodes, and enlargement of salivary glands.
3. Oropharyngeal form – This variant manifests as ulcerative-exudative stomatitis and pharyngitis, hypertrophy of palatine tonsils and local lymph node tenderness.
4. Respiratory tularemia – Bronchopneumonia or pneumonia lead to respiratory failure without prompt and proper treatment. Pneumonic abscesses may occur. Mortality rate in this form reaches 30–60% of untreated patients.
5. Typhoidal tularemia – High fever and lymph node enlargement without any primary lesion of the skin or mucous membrane is characteristic of this form [11].
6. Intestinal form – In this form stomach ache, diarrhea and intestine ulcers dominate [2].

The most common complications of Tularemia include meningitis, encephalitis, peritonitis, purulent arthritis, endocarditis, thrombophlebitis, liver and kidneys failure, and sepsis [1, 4]. The differential diagnosis includes tuberculosis, mononucleosis, cytomegaloviral infection, cat scratch disease, bacterial pharyngitis, diphtheria, Hodgkin lymphoma, typhoid, pneumonia, brucellosis, mumps, plague, toxoplasmosis, syphilis, HIV infection, and influenza [4]. Difficulties in making the correct diagnosis



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are connected to the variety of clinical manifestations. Delayed hospitalization and inappropriate treatment with misdiagnosis may increase the likelihood of development of complications of tularemia. The mortality rate in cases without any treatment is approximately 5%. Recovery time is very long.

The presumptive diagnosis should be based on epidemiological and clinical findings and the final microbiological confirmation. The most commonly used diagnostic method is serological testing – ELISA and Western blot in which antibodies IgM, IgG can be detected. PCR method is based on molecular detection of DNA. The culture provides a conclusive diagnosis and grows out the appropriate antibiogram, however, isolation of bacteria may be problematic. When it is impossible, PCR should be run. In cases of prolonged diagnosis – as with our case- the best solution is detection of specific antibodies with ELISA [4]. In uncertain cases, agglutination test should be done.

The drug of choice is intravenous Gentamycin (5 mg/kg/day divided in two doses) or Streptomycin (2 g daily in two divided doses), although the drug is no longer widely used due to its ototoxicity. Additionally doxycycline may be used. In mild disease, fluoroquinolones – such as Ciprofloxacin (orally or intravenously 800–1000 mg daily) may be administered. When dealing with tularemia in children, the first line drug is also Gentamycin (5–6 mg/kg daily) or Streptomycin (15 mg/kg daily). In pregnant woman, despite the toxic adverse effect, Gentamycin or Cipro-

floxacin is recommended in the same dosage as in non-pregnant adults [11]. New drugs should be invented and research should be conducted to determine alternative agents for treating this condition, especially in children and pregnant woman. In vitro studies shows good effectiveness of the following drugs: Fluoroquinolones (Moxifloxacin, Gatifloxacin, Trovafloxacin, Grepafloxacin) as well as Ketolids (Telitromycin, Cethromycin) and Tygacycline [3]. At present, tularemia vaccine research is being carried out in the USA and Europe in hopes of protecting exposed individuals from the disease [9]. In Poland, tularemia is not a relevant problem, however, a few cases are registered each year, mostly in the northeast part of the country. Efforts to combat the pathogen are made via systematic deratization of farms, as well as securing of grain, food, and water from rodent and insects. Non-compliance with safety and hygiene rules on farms, in forests, laboratories, leather binding, and with burial of animals has thwarted progress in eradicating this disease. In Poland, tularemia cases are subject to compulsory notification, registration, and treatment. This zoonosis is covered by veterinary regulations and a statute of eradication and prevention of infectious disease. *Francisella tularensis* is used as an agent for

bioterrorism. According to a WHO report from 1970, pulverization of 50 kg of tularemia bacillus could cause a morbidity of 250,000 individuals and mortality of 19,000 victims if dispersed among a population of approximately 5 million [6, 11]. Because our patient was breeding cows and rabbits on a farm, she could have potentially been exposed to at least 2 types of zoonosis – brucellosis and tularemia. The fact that she was breeding cows; was preparing dairy products from milk; and that one of her cows had a miscarriage put her at risk for infection by *Brucella abortus*. If we take into consideration her breeding rabbits, eating rabbit meat, cleaning cages, or playing with rabbits, this patient was additionally at risk for infection by *Francisella tularensis*. Tularemia is a rarely occurring disease in Poland. The morbidity rate reached 9 cases in 2015 and 18 patients in 2016 [7]. In most ENT departments, it is hardly ever taken into consideration during the diagnostic process in patients with neck lymphadenopathy. In clinical practice otorhinolaryngologists should always remember about this infectious zoonosis and especially about the oculoglandular and oropharyngeal form because delayed diagnosis and treatment may cause serious health consequences in our patients.

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