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Glandural turemia of the neck in a 18-year old women

Tularemia węzłowa szyi u 18-letniej pacjentki

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ABSTRACT: Tularemia is a rare zoonosis disease caused by Gram-negative, aerobic bacilli—*Francisella tularensis*. The most frequent contamination route is percutaneous, by mucous membranes, inhalation or ingestion. The main reservoir of tularemia are animals: rabbits, hares, mice and squirrels, which are infected by an insect bites (ticks, mosquito, fly) or contact with contaminated soil or water. Tularemia has many clinical forms. Serological and molecular tests are necessary. Treatment is based on not empiric antibiotic (streptomycin, gentamicin). The aim of the study is to present the case of neck lymphadenopathy (glandular type of tularaemia) in a young woman and encountered diagnostic and therapeutic problems.

KEYWORDS: *Francisella tularenis*, neck lymphadenopathy, tularemia

STRESZCZENIE: Tularemia jest rzadką chorobą odzwierzęcą, spowodowaną tlenową, Gram-ujemną pałeczką *Francisella tularensis*. Do zakażenia człowieka najczęściej dochodzi przypadkowo: drogą przezskórną, przez błony śluzowe, drogą wziewną lub pokarmową. Głównym rezerwuarem pałeczek tularemii są: zające, króliki, myszy i wiewiórki, ulegające zakażeniu po ukłuciu przez zakażone owady (kleszcze, muchy, komary) oraz przez kontakt z zanieczyszczoną glebą lub wodą [1–6]. Wyróżnia się kilka postaci klinicznych tularemii. Manifestacja kliniczna i obraz radiologiczny nie dają jednoznacznego rozpoznania, dlatego niezbędna jest diagnostyka serologiczna i/lub molekularna. Leczenie opiera się na rzadko stosowanych empirycznie antybiotykach (streptomycyna, gentamycyna). Celem niniejszej pracy jest przedstawienie trudności diagnostyczno-terapeutycznych tularemii na przykładzie przebiegu choroby i leczenia młodej pacjentki z limphadenopatią szyjną.

SŁOWA KLUCZOWE: *Francisella tularenis*, limfadenopatia szyjna, tularemia

INTRODUCTION

Tularemia is a zoonotic infectious disease also known as: rodent plague, hare disease or rabbit fever [6]. The disease is caused by an aerobic, gram-negative intracellular bacilli – Francisella tularenis [1–10]. The name of the bacterium derives from the name of American researcher Edward Francis [3]. Although the disease is rare, it is still a serious epidemiological problem due to its high infectivity [5, 7]. According to the European Centre for Disease Prevention and Control (ECDC), the incidence of tularemia in Europe in 2006–2010 remained more or less stable, around 900 cases per year, mainly in Sweden, Finland and Hungary [3]. In Poland, tularemia was first recognised in 1949 in Łódź – the source was probably hare skin. Since then, over 600 cases have been recorded mainly in the north-west and north-eastern voivodships. In 2015–2016, the Chief Sanitary Inspectorate recorded a doubling of registered applications from 9 to 18 patients [7]. Due to the difficulty in recognising the disease and low declaration rates, it can be assumed that the number is even higher. It is worth mentioning that in Poland it has been subject to registration and hospital treatment since 1963 [6].

Tularemia is a difficult to diagnose contagious disease. Due to the multitude of forms, non-specific symptoms and difficult diagnostics, it is a challenge for many doctors, including ENT specialists. Only a few cases of various forms of tularemia have been described in the native ENT literature [3, 8, 9]. All authors agree that in the case of nonspecific cervical lymphadenopathy it is necessary to take into account this disease in differentiation.

CASE REPORT

An 18-year-old patient was admitted to the Department of Adult and Paediatric Otolaryngology and Otolaryngological Oncology Clinic of the Pomeranian Medical University because of angina

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with severe right-sided nodular reaction. During history taking, the patient reported a severe sore throat and fever up to 38.7 degrees Celsius persisting for over 10 days. In addition, painful cervical lymph nodes enlarged for a week – mainly right-sided. Admitted due to lack of improvement after empiric outpatient antibiotic therapy (amoxicillin/clavulanic acid, followed by azithromycin).

Based on the patient's medical history, chronic diseases, allergies and injuries to this region were excluded. The patient did not take regular medications. Socioeconomic status was assessed as good. Before the illness, she was in a horse-riding camp, where she had contact with horses, dogs, and arthropods and insects attacking them.

On the day of admission, the patient was in a good general condition. On physical examination the patient had: significantly enlarged, red palatine tonsils, a cheese-like white coating was present on both sides of the tonsils on the medial surface. Symmetrical palatoglossal arch, without features of peritonsillar abscess. Trismus was not observed. Lymph node packages with size of 3 x 4 cm, firm lymph nodes, painful at palpation, mobile relative to the substrate, numerous small nodes in the vicinity. Numerous, small, reactive lymph nodes also revealed on the left side. Other peripheral lymph nodes were not enlarged. Vesicular murmur above lung fields was found to be normal. Heart activity was rhythmic. Soft, painless abdomen, liver and spleen not enlarged.

Laboratory testing of the blood showed signs of inflammation: increased leukocytosis – 10.59 thou./ul and high CRP values – 105.33 mg/l and OB 105 mm/h. During hospitalisation diagnostics were expanded to include tests for Epstein-Barr and HIV infection that were negative.

Ultrasound examination of the neck performed at admission described a lymph node package in the right angle of the mandible sized 21 x 37 mm and a heterogeneous area in the central area – decay could not be ruled out (Fig. 1.). Furthermore, there were numerous lymph nodes on the right side in fields II, III, IV and V with blurred hilum. On the left side there were several hypoechoic lymph nodes in fields II, III and IV also with blurred hilum.

Ultrasound examination of peripheral lymph nodes showed quite numerous lymph nodes in both axillary cavities, with predominance on the right side, with correct morphology. Small, not enlarged, normal lymph nodes in both groins.

Chest X-ray showed no pathological changes.

During hospitalisation, empiric intravenous antibiotic therapy (amoxicillin/clavulanic acid) was continued, after which resolution of pharyngitis and normalisation of inflammation parameters in laboratory tests were observed. However, no regression of nodal changes was observed.

For the above reasons, imaging diagnostics were expanded to include contrast-enhanced magnetic resonance imaging of the neck followed by fine needle aspiration biopsy. Magnetic Resonance Imaging in the posterior cervical space showed a nonuniform, pathologic lesion sized 26 x 22 x 17 mm enhancing after administration of contrast medium. An irregular fluid space indicating breakdown was found inside the lesion. The described lesion adhered to surrounding structures and vessels, without infiltration and bone destruction (Fig. 2.). On the other hand, cytological evaluation of the biopsy showed almost exclusively necrotic lesions in the examined material.

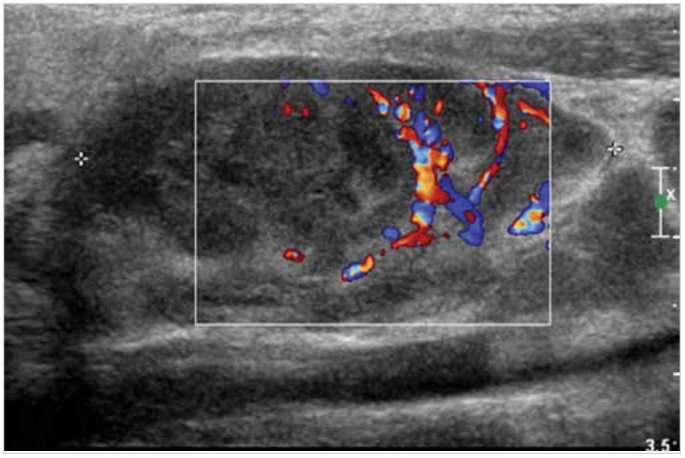

Fig. 1. Doppler ultrasound – lymph node package with signs of decay.

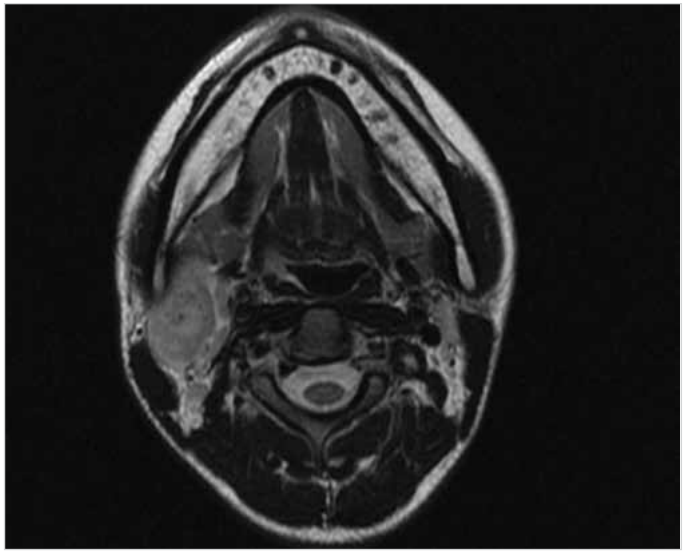

Fig. 2. Magnetic Resonance Imaging – a pathologic lesion sized 26 x 22 x 17 mm was observed in the posterior cervical space.

Due to a negative FNA result, the patient was qualified for lymph node removal for histopathological verification. A large packet of lymph nodes was found intraoperatively on the right side with numerous smaller lymph nodes around. During dissection, the largest node was fragmented with the evacuation of purulent contents. Histopathological examination showed irregular fragments of lymphatic tissue with the presence of epithelioid granulomas Langhans giant cells, necrosis in the centre and sometimes with the presence of neutrophils. Additional tests for the presence of mycobacteria with the Ziehl-Neelsen stain were negative and tuberculosis was most likely ruled out on this basis. Sarcoidosis and erythroleukemia were also excluded. The histological picture was finally assessed as corresponding to granulomatous inflammation. Cytrometry of the material revealed no cells with a tumour immunophenotype.

After surgery the patient was generally in good condition, no complications in postoperative period were observed. Due to the unclear background of cervical lymphadenopathy, the patient was transferred to the Department of Infectious, Tropical Diseases and Acquired Immune Deficiencies of the Public Independent Consolidated Voivodship Hospital in Szczecin for further diagnostics. Subsequent studies excluded infection with: Toxoplasma gondii, Yersinia enterocolitica, Borrelia burgdorferi, Toxocara canis, Treponema pallidum, while serological tests performed at the Department of Bacteriology at NIZP-PZH confirmed the presence of antibodies to F. tularensis antigens. Antibiotic therapy was instituted in the form of Ciprofloxacin 2 x 500 mg, alternating with Doxycycline for local improvement. Due to the very young age of the patient, streptomycin was not used. The patient stays under clinical control at the Infectious Disease Clinic. At an interval of 1.5 months, she reported three more times to the Admissions Department of the Observation Ward due to enlarged lymph nodes on the right side (administration of Doxycycline was continued).

DISCUSSION

Tularemia is a rarely diagnosed zoonosis. Human infection is most often accidental: transdermal, mucosal, by inhalation or ingestion. The main reservoir for tularemia are hares, rabbits, mice and squirrels, which become infected after being stung by infected insects (ticks, flies, mosquitoes) and by contact with contaminated soil or water [1–6]. No human-to-human infections were recorded. People who have direct contact with sick animals (foresters, hunters, butchers, farmers, breeders, veterinarians) are most often infected. It was noted that the majority of cases were recorded in the summer months, which is associated with greater activity of mosquitoes, flies and ticks (tourists) [1, 2 ,4]. The patient presented above was a resident of a small town near Szczecin in the West Pomeranian Voivodeship. She had contact with animals (horses, rabbits) every day, but she negated any injury, scratching, or the possibility of eating contaminated food. An insect bite was considered the most likely route of infection.

Depending on the portal of entry of the microorganism, several clinical forms of tularemia have been described. The most common is ulcerograndular type, which in Europe accounts for about 95% of cases [1, 3–5, 8]. In our case, erythematous papules form at the portal of entry of the microorganism, which in 2–3 days transform into pustules, followed by ulcers and sometimes fistulas. 3–6 days after exposure, flu-like symptoms appear. Bacteria from the portal of entry penetrate into the lymph nodes and into internal organs, including the lungs, liver, spleen, kidneys, skeletal muscles or the central nervous system [5, 6]. The glandular type proceeds similarly, however, the patient's condition is not as severe as in the previous case, and there are no ulcers or fistulas on the skin [3, 5, 6, 9].

The oculoglandular type is rare (about 1% of infections). Infection occurs by transfer of infectious bacilli from the skin of the hands to the eyes, which causes severe unilateral conjunctivitis with ulceration and reaction from lymph nodes (preauricular, cervical and submandibular) and enlargement of salivary glands [3, 4, 8].

The oropharyngeal (angina) type constitutes about 5%. This type appears after eating contaminated food, water, or after aerosol aspiration. It occurs with exudative stomatitis, pharyngitis and/or tonsillitis and enlarged cervical lymph nodes. It may suggest streptococcal angina [3,6,8].

Pneumonic (primary) tularemia is rare. It occurs as a result of contamination by inhalation. It is more often observed as a secondary form in the course of ulceroglandular and pharyngoglandular infection. The course of illness can be difficult. Non-specific symptoms: chest pains, dry cough, high fever. The most characteristic symptom is enlarged axillary nodes. Chest x-ray may show enhanced follicular density, granulomatous lesions or abscesses. Mortality in untreated cases can reach up to 30–60% [3, 5, 6]. The visceral (gastrointestinal) is characterised with severe course with high fever, abdominal pain, diarrhoea. No skin or mucosal lesions are found in this form.

The typhoidal (septic) form is the most severe and least characteristic. The route of infection is unknown. The patient has a high fever, no skin changes or nodal reaction occur. In this case, shock, multiple organ failure, meningitis, rhabdomyolysis or disseminated intravascular coagulation syndrome may occur [1–3, 5, 7, 8, 10–12]. Mortality in this form reaches 50%.

Serious complications can occur in the course of tularemia. The most common are meningitis and encephalitis, exudative peritonitis, arthritis, pericarditis and endocarditis, thrombophlebitis and liver, kidney and sepsis failure [8].

Our patient showed symptoms of a glandular form of tularemia. Empirical treatment (amoxicillin/clavulanic acid and azithromycin) did not bring any significant clinical improvement. Diagnostics excluded neoplastic process, nonspecific inflammation, tuberculosis, HIV, mononucleosis and sarcoidosis. The final diagnosis was made as a result of serological diagnostics for zoonoses at the Observation Ward. In the opinion of many authors, diagnosis of tularemia is difficult and is usually based on medical history, clinical picture and serological and/or genetic tests [4]. This was also the case with our patient. It should be remembered that in the diagnosis of tularemia, serological tests, i.e. serum agglutination test and microagglutination test, ELISA tests, latex tests and western blot method are used [6]. Samples for analysis are usually taken twice, at the beginning of the disease and after 2–4 weeks, due to numerous cross-reactions and false positive results. Specific laboratory antibodies are sought for F. tularenis. It is worth emphasising that serological tests are characterised by high sensitivity and specificity. Antibodies appear 10–14 days after the onset of clinical symptoms, reaching their highest levels after 4–7 weeks [4]. Bacteriological diagnosis of tularemia is difficult. Breeding must be carried out on specific enriched media in specialised reference centres due to the high infectious potential and ease of spread of tularemia. Tularemia bacillus is mentioned, after anthrax and botulinum bacteria, among the microbial agents that can be used in bioterrorism [2, 5, 8, 13].

Material from biopsies, lymph nodes, sputum or throat swab can be used to grow bacteria. Blood cultures usually give negative results.

Molecular studies (by PCR) are also a specific and useful technique – however, they have limited availability [1, 3–5, 11, 14]. Molecular studies allow the typing of different F. tularenis strains. According to the literature, DNA microarray is also used to identify *F. tularenis*, which allows for obtaining a large amount of information on gene expression, mutation, polymorphism or degree of relatedness [4].

Histopathological examination does not give an unambiguous diagnosis. The dominant picture is granulomatous inflammation, with tuberculous-like granulomas and multinucleate giant cells. Therefore, the picture differentiates primarily from tuberculosis, cat-scratch disease and sarcoidosis [2, 3, 5, 8, 11, 14]. In our patient's case, the histopathological picture corresponded to granulomatous inflammation. Mycobacterial tests gave negative results, which allowed to exclude tuberculosis with high probability. Sarcoidosis was also excluded. In this situation, it was reasonable to transfer the patient to the infectious disease clinic to exclude zoonoses.

In the treatment of Tularemia, aminoglycoside and fluoroquinolone are most commonly used, and the duration of administration depends on the severity and course of infection [1, 2, 5, 8, 14]. In accordance with WHO recommendations, the first-line treatment is Streptomycin 15 mg/kg body weight/day or Gentamicin 5–6 mg/kg body weight/day in two divided doses for 10 days. Quinoline-Ciprofloxacin 15mg/kg body weight twice daily for 7–10 days or Doxycycline 100 mg orally 2x daily for 14 days are used in refractory and relapsed cases, or massive outbreak of disease. In children, Gentamicin or Streptomycin are also the drug of choice. Despite the toxic effects of Gentamicin and Doxycycline, the use of these drugs is also recommended for pregnant women [15]. In our patient, treatment was started with empirical antibiotic therapy, which did not give the desired effect. After starting treatment with Ciprofloxacin, then Doxycycline, the patient's condition improved significantly. Doxycycline treatment was continued for an extended period due to persisting lymphadenopathy.

Some hope for reducing the incidence of these dangerous zoonosis is associated with the immunisation of occupationally exposed staff in areas such as forestry, agriculture, veterinary medicine, etc. Research into vaccine development is underway in Europe and the US. The only live attenuated LVS vaccine is not widely available [6, 8].

One should not forget about the prevention of tularemia by neutralising the sources of infection and thus systematic and effective control of field rodents and ticks, as well as compliance with health and safety rules in agriculture and forestry [6].

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