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ULCEROGLANDULAR TULAREMIA COMPLICATED BY PNEUMONIA - A CASE REPORT

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ABSTRACT

Tularemia is an antropozoonosis caused by Gram-negative coccobacillus *Francisella tularensis.* The majority of tularemia cases are reported in summer due to exposure to insect and tick bites. This paper discusses a case of 11-year-old boy diagnosed with ulceroglandular tularemia complicated by pneumonia.
Conclusions: tularemia should be considered in differential diagnosis of febrile condition and lymphadenopathy in children who contracted disease in summer or autumn, especially if there is a history of insect or tick bite.

Key words*: tularemia, fever, insect or tick bite*

INTRODUCTION

Tularemia is an antropozoonosis caused by aerobic Gram-negative coccobacillus *Francisella tularensis*. This bacterium was first isolated in 1911 in California. Its name origins from the surname of scientist – *dr Edward Francis*. This bacterium is characterized by the ease of spreading, high virulence and infectivity. Only 10 colony forming units (CFU) constitute an infective dose for humans (1). Therefore, *F. tularensis* is enumerated as third, following *Bacillus anthracis* and *Clostridium botulinum* as the possible biological agent to be used in a terroristic attack (2).

Infection is most commonly transmitted due to contact with infected animal or contaminated animal tissues or through bites of infected insect or tick. Bloodsucking ticks and insects are the vectors of infection while reservoirs constitute wild forest and field rodents and wild fowl. Infection may also occur through inhalation of infective aerosols, oral exposure and through conjunctiva.

Tularemia may be present as sporadic infections or occur epidemically, most frequently in summer which should be linked with seasonal activity of insects and ticks. Tularemia is usually reported in the countries of the northern hemisphere, i.e. Scandinavia, North America, Japan and Russia (3-7).

The highest prevalence of tularemia worldwide was noted in 1930-1950. Epidemics occurred due to exposure to contaminated water. In Poland, a total of 614 tularemia cases were reported in 1946-2009 with one fatal case noted in 1983 (8). Nowadays, sporadic cases of tularemia are reported in Poland: 4 and 6 cases were notified in 2010 and 2011, respectively. In the majority of cases (98%), humans became infected through contact with hares (9,10). However, taking into account the appearance of non-specific symptoms in infections of mild or asymptomatic course as well as insufficient laboratory testing, the number of tularemia cases may be underestimated (11).

Typically, there is an abrupt onset of disease, accompanied by high fever, chills, headache, arthralgia and myalgia. Incubation period for tularemia ranges from 2 days to 3 weeks. Following an exposure to insect or tick, a skin ulcer and inflammation are present at the site of bite. Then, pyogenic and granulomatous skin lesions appear which may resemble lesions indicative of tuberculosis. In case of untreated patients, fever is of recurrent nature.

Having considered bacterium entrance site, its virulence and infective dose, several clinical manifestations of tularemia may be enumerated. Ulceroglandular and glandular forms of tularemia account for ca 85% of all cases. Other infections occur as anginal, oropharyn-

geal, pneumonic, oculoglandular or typhoidal forms (11). Infected patients are not required to be isolated as human-to-human transmission of tularemia has not been reported.

According to the *Working Group on Civilian Biodefense,* streptomycin and gentamicin administered for 10 days are the drugs of choice in the treatment of tularemia. Alternatively, doxycycline and chloramphenicol or ciprofloxacin are to be applied for 14-21 and 10 days, respectively. *Sanford* states that trimethoprim/sulfamethoxazole may also be used (12,13).

Below a case of 11-year-old boy who was diagnosed with ulceroglandular tularemia complicated by pneumonia was discussed.

CASE PRESENTATION

A 11-year-old boy (M.K. medical record No. 5094/1166/12, height 151 cm, body weight 54 kg) residing in Kujawsko-pomorskie province, in Sośno commune presented with a fever exceeding 39^0C in the first days of September 2012. Patient did not complain of any health problems. Except for fever, none symptoms were observed. After 11 days from the onset and following out-patient therapy with second-generation cephalosporin, the patient was referred to district hospital due to prolonged fever up to 40^0C. On admission, he had a slight limp in the left leg and cough. Physical examination revealed a lump on the left shin and two enlarged, tender lymph nodes in the left groin. Auscultation showed sounds over the lung field in the form of medium crackles. It was determined that skin lesion on the left shin was present since 3 weeks and it appeared after the gadfly bite. Therapy with clarithromycin, cefotaxime and clindamycin was continued for the next 11 days. During hospitalization, the boy had a fever up to 39^0C. Despite the regression of sounds over the lung field and normal chest radiography, slight cough was observed. Inflammation of lymph nodes in the left groin remained and ulcer appeared at the site of lump. In accessory investigations, parameters indicative of acute inflammation decreased: leukocytosis from 19.21 K/ul to 14.6 K/ul, CRP from 106 mg/l to 40 mg/l. Ultrasound of abdominal cavity and ECG did not reveal any abnormalities. Throat and urine cultures were negative.

As there was no clinical improvement, patients was moved to the Provincial Infectious Diseases Observatory Hospital in Bydgoszcz to differentiate febrile condition.

On admission to the hospital ward, the boy presented with 3-week-fever, limp in the left leg and slight cough without any sounds over the lung field in auscultation. Physical examination revealed an ulcer of 15 mm in diameter on the posterior surface of the left shin, two lymph nodes enlarged to 15 mm in the left groin and tender infiltration (50x60 mm) on the anteromedial surface of the left shin, below the inguinal ligament. Ultrasound showed hypoechogenic enlarged lymph nodes and infiltration on the shin as noncapsulated liquid container in the form of abscess. Laboratory testing revealed abnormalities such as leukocytosis $15.8x10^3$uL and elevated CRP of 60.2 mg/l.

Based on the patient's history, physical examination and accessory investigations, preliminary diagnosis of acute lymphadenitis in the course of bacterial infection complicated by an abscess of left thigh was determined. Infections with the following agents: EBV, CMV, HBV, HCV, HIV, *Mycoplasma pneumoniae, Bordetella pertussis, Treponema pallidum, Bartonella henselae* and *Toxoplasma gondi* were excluded. An interferon-gamma release assay (T-SPOT), RT 23 and the culture of smear collected from the left shin ulcer were negative.

Having considered gadfly bite in the patient's history which preceded the appearance of ulcer, samples were collected for tularemia testing.

On day 9 of antimicrobial therapy, a decrease of parameters of acute inflammation (CRP to 24.9 mg/l, leukocytosis to $12.43x10^3$uL) was observed and shin ulcer was healed. However, tender infiltration on the left thigh was enhanced. Multicellular abscess was removed, using surgical intervention and 30ml of sterile fluid was evacuated. An excision of lymph node from the left groin and subcutaneous tissues for histopathology was performed. Investigations showed chronic granulomatous inflammation with necrotic subcutaneous tissues and granulomatous lesions with necrosis indicative of tuberculosis.

Chest CT scan revealed enlarged mediastinal lymph nodes: 8 mm paratracheal lymph node on the right side and 9 mm lymph nodes in recesses on both sides, tracheoesophageal fistula of 2 mm wide at neck and chest line and interstitial lesions in the lower lobes of the lung in the form of matt glass and reticular densities, indicative of inflammation and enlarged axillary lymph nodes on the right and left side to 12 mm.

Esophagogastroduodenoscopy (EGD) was performed to obtain gastric contents to be tested for the presence of DNA of *Mycobacterium tuberculosis.* Examination confirmed tracheoesophageal fistula on the anterior wall of oesophagus, below the first area of physiologic narrowing (Photo 1). Test results for the presence of genetic material of *Mycobacterium tuberculosis* and acid-fast bacillus (AFB smear) in gastric juice and fluid collected from abscess and adjacent tissues were negative.

Serology was positive for IgA, IgM and IgG antibodies coccobacillus *F.tularensis* antigens by immunoenzymatic assay ELISA (two samples of serum collected in weeks 4 and 7 followings infection). Test-

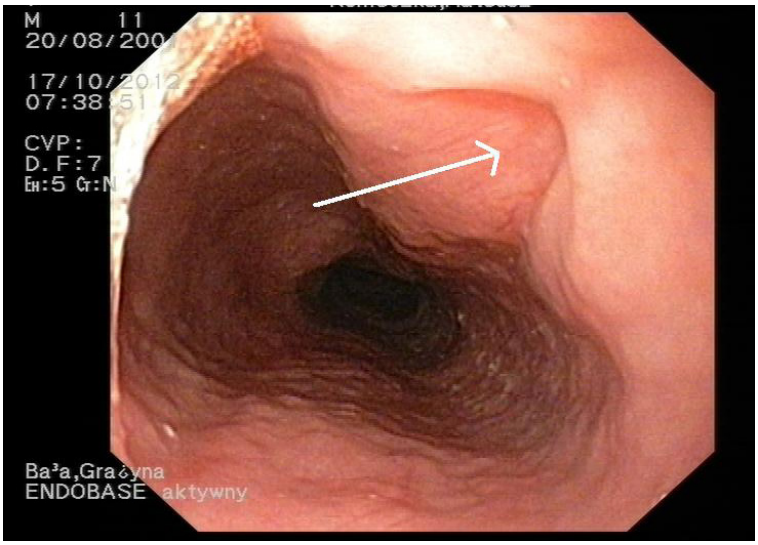

Photo 1. Tracheoesophageal fistula.

ing was performed in the National Institute of Public Health-National Institute of Hygiene in Warsaw.

Combined antimicrobial therapy was applied: initially gentamicin was administered in a dose of 5 mg/kg/day, every 12 hours intravenously and amoxicillin with clavulanic acid – 1.2 g every 8 hours iv for 7 days, then ceftriaxone 1x2.0g/ day for 6 days and trimethoprim/sulfamethoxazole - 2x 960 mg orally for 10 days. During hospitalization in the Provincial Hospital, the boy had no fever beginning from the second day of therapy and he did not complain of any pains. He still presented with slight, non-productive cough. Following therapy, CRP and the number of leukocytes were within normal limits.

Further diagnostics and treatment of fistula were determined in the Institute for Tuberculosis and Lung Diseases in Rabka. Bronchofiberoscopy showed tracheoesophageal fistula whose external diameter was 49 mm and orifice situated at a distance of 7-8 cm from rima glottidis. Boy was qualified for right-sided thoracotomy aimed at closure of fistula.

After several weeks from thoracotomy, patient was consulted again in our hospital. He did not complain of any health problems and had no cough.

DISCUSSION

Glandular form of tularemia in children is usually present as lymphadenopathy of cervical and postauricular lymph nodes which corresponds to an exposure to tick and insect bites in the head and neck region while in adults it appears as inguinal-femoral lymphadenopathy resulting from exposed lower limbs. Initially, an itchy lump appears at the site of bite which a few days later progresses into an ulcer. Local lymph nodes are subject to enlargement. In ca 25% of patients, suppuration of lymph nodes appears and examination reveals sterile necrotic tissue in the material collected from affected node (14). Similarly, histopathology of thigh tissue fragment showed inflammatory infiltration and extensive areas of necrosis. Lesions were described as hardly indicative of tuberculosis. Thus, testing for mycobacteriosis was recommended.

Diagnosis of tularemia is difficult. It can only be performed in laboratories meeting the criteria of Biosafety Level 2 (BSL-2) as the samples should be considered as highly infectious material. Materials for laboratory testing include blood, urine, lymph node or lesion bioptates, throat swab, pleural effusion and specimens of contaminated food and water. Microscopic or histological sections, serologic testing, biological tests, culture and genetic testing may also be performed. However, its routine use is associated with many limitations. The majority of tularemia cases are diagnosed based on clinical picture and serologic testing. In a case of patient described, the presence of IgA, IgM and IgG antibodies to *F.tularensis* was detected by ELISA. Clinical picture was indicative of ulceroglandular form.

It should not be forgotten that serologic testing may be negative for the first 7-14 days of infection. Therefore, diagnosis and therapeutic success depend on proper medical history taking and physical examination. Infections of mild or oligosymptomatic course cause diagnostic difficulties and in some cases ulcers located in the groin or neck region may not be noticed by parents.

Presence of skin lesion with accompanying local lymphadenopathy should be considered for differential diagnosis with bacterial infections (*S.aureus, S.pyogenes*), cat scratch disease, tuberculosis, infection with nontuberculous mycobacteria, syphilis, toxoplasmosis and anthrax.

Pneumonic form of tularemia accounts for nearly 5% of cases in adults and children. Persons are infected

due to inhalation of pathogens or through bloodborne route in 10-15% of ulceroglandular tularemia cases. Clinical manifestations of pneumonic tularemia are not of specific nature. Thus, it is difficult to differentiate tularemia clinically or radiologically from other atypical pneumonia.

In a case of patient analyzed, in the initial phase of disease, sounds over the lung field in the form of medium crackles were observed and then boy had a slight non-productive cough. Persistent cough could result from tracheoesophageal fistula or a history of pneumonia. Diagnosis of ulceroglandular tularemia complicated by pneumonia is motivated by the clinical course of disease, interstitial lesions in the lungs with enlargement of mediastinal lymph nodes and exclusion of other atypical pneumonia.

Aminoglycosides are recommended in the treatment of infections with *F.tularensis*. In case of children, gentamicin is applied for 7 to 10 days. Effective treatment leads to the regression of fever within two days which is confirmed by own observation. Initiation of such therapy in the first three weeks following infection prevents from complications such as suppuration of lymph nodes (15). In a case of patient analyzed, empiric 7-day therapy with gentamicin was initiated on day 23 of infection and second day. As it was expected, fever decreased to below 37^0C. No suppuration of lymph nodes in the left groin was observed. However, treatment initiated in week 4 of infection did not prevent from thigh inflammation resembling multicellular abscess.

Assumption that tularemia occurs rarely contributes to the situation in which this condition is seldom suspected by clinicians. However, it should be presumed that infections with coccobacillus *F.tularensis* occur significantly more frequently in the population compared to the number of notified cases.

History of patient analyzed demonstrates that tularemia should be considered in the differential diagnosis of febrile conditions accompanied by enlargement of lymph nodes in children, especially in summer and early autumn and if there is a history of contact with confirmed animal tularemia vector. Early diagnosis and targeted antimicrobial therapy are a basis of effective treatment.

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