

Erythema multiforme and erythema nodosum lesions with cervical lymphadenopathy

Ümran Muslu¹, Engin Şenel^{2,3}, Yasemin Y. Karabulut⁴

¹ Hitit University Faculty of Medicine, Department of Plastic Aesthetic and Reconstructive Surgery, Çorum, Turkey

² Hitit University Faculty of Medicine, Department of Dermatology, Çorum, Turkey

³ Hitit University, Beekeeping and Bee Products Application and Research Center, Çorum, Turkey

⁴ University Faculty of Medicine, Department of Pathology, Mersin, Turkey

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Corresponding author: Ümran Muslu, MD, Assistant Professor of Plastic, Aesthetic and Reconstructive Surgery, Hitit University Faculty of Medicine, 19200 Çorum, Turkey. Tel. +90 364 2230300; Fax +90 364 2230323. Email: umrandr@hotmail.com

The patient

A 39-year-old otherwise healthy woman presented to our dermatology clinic with a two-week history of a swelling and pain on her neck. She noted a low-grade fever and malaise for ten days. The patient reported no history of tick bite, new medication or consuming raw meat. Physical examination revealed fever (38.3°C), an enlarged, painful 4.5 x 4.8 cm sized lymphadenopathy in the right submandibular area (Figure 1), multiple targetoid erythema multiforme lesions on the palms (Figure 2), and multiple erythema nodosum lesions on the shins (Figure 3). We performed whole blood count, chest X-ray, serological tests (microagglutination test), fine needle biopsy, and neck ultrasonography. Histopathologic examination of the lymph node disclosed epithelioid histiocytes with multinuclear giant cells and a suppurative inflammation (Figure 4a and 4b).



Figure 1. Right submandibular lymphadenopathy. [Copyright: ©2017 Muslu et al.]

What is your diagnosis?



Figure 2. Targetoid erythema multiforme lesions. [Copyright: ©2017 Muslu et al.]



Figure 3. Multiple erythematous subcutaneous nodules on anterior tibias. [Copyright: ©2017 Muslu et al.]

Answer

Tularemia

Serum sample of the patient was obtained and microagglutination test was performed for tularemia serology. The diagnosis of oropharyngeal tularemia was confirmed by an antibody titer of 1:320.

Discussion

Tularemia, also known as “rabbit fever” and “deer fly fever,” is a bacterial zoonosis caused by a gram-negative, aerobic and intracellular coccobacillus, *Francisella tularensis*. Four subspecies of the bacterium were recognized: *tularensis*, *holarctica*, *novicida* and *mediasiatica*. The most virulent subspecies is *tularensis* (Jellison type A) and has the highest human mortality rate [1]. Subspecies *holarctica* (Jellison type B) that causes a less severe form of the disease is responsible for the infections in Europe and Asia.

Tularemia was first described in 1911 in Tulare County in the U.S. state of California. The incubation period of the disease is 3-5 days (range: 1-21 days) [2]. Tularemia is a

potentially fatal disease in the northern hemisphere [3]. Clinical findings of tularemia vary according to the bacteria’s entry place into the host, virulence, the dose of inoculation and the immunological status of the host. According to these factors, the disease is classified into six major clinical forms, namely oropharyngeal, ulceroglandular, glandular, oculoglandular, typhoid and pneumonic tularemia. Oropharyngeal tularemia is caused by bacterial infiltration from the oral mucosa due to ingestion of contaminant foods and waters. Fever, sore throat, and inflammation of the oropharyngeal area occurs. Unilateral or bilateral lymphadenopathy develops in the neck. The patients are diagnosed wrongly with acute streptococcal tonsillopharyngitis and treated unsuccessfully with beta-lactam antibiotics. The most common complication in this form is lymph node suppuration. Skin lesions and lymphadenopathy following contact with an infected animal or tick bite should suggest an ulceroglandular form of tularemia. In glandular form, the entry site of the bacteria into the host is not known and the patient has tender lymphadenopathy and fever. Oculoglandular tularemia develops after conjunctival inoculation or contamination with water. This form is accompanied by

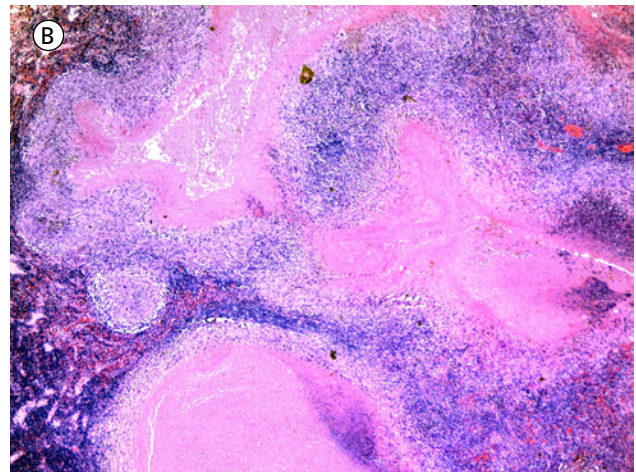
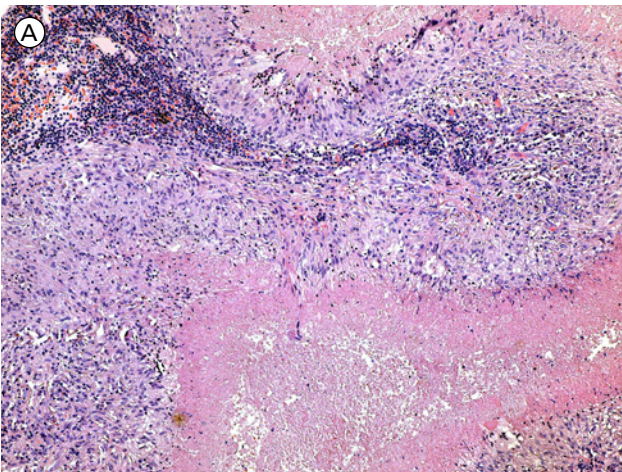


Figure 4a, b. Epithelioid histiocytes with multinuclear giant cell and a suppurative inflammation (H&E x40 and H&E x100). [Copyright: ©2017 Muslu et al.]

unilateral, rather painful, purulent conjunctivitis and tender lymphadenopathy. The pneumatic form develops primarily due to inhalation of infectious aerosols (primary pleuropulmonary disease) or hematogenous spread of bacteria during other forms of tularemia. In typhoid tularemia, the entry site of the bacteria could not be found and there is no lymphadenopathy. It is a systemic disease frequently causing pneumonia, meningitis, hepatitis, carditis (relative bradycardia), and nephropathy. Our case was identified as oropharyngeal tularemia, which is the most common form in our country.

The differential diagnoses of masses in the neck include infections causing unilateral lymphadenopathy, lymphoma, metastasis of malignancies of head and neck region. Primary malign lesions can be identified in 65% of the cases with a detailed and sufficient anamnesis and a thorough pharyngeal examination. If the mass does not seem to be related to malignancy, laboratory tests for lymphoma should be ordered to avoid time loss [4,5]. Acute viral lymphadenopathies (EBV, rubella, CMV), acute bacterial lymphadenopathies (*Streptococcus pyogenes*, *Staphylococcus aureus*, group B streptococci, anaerobic bacteria, *Yersinia pestis*, *Francisella tularensis*, *Pasteurella multocida*, *Haemophilus influenzae* type b, etc.), subacute and chronic lymphadenopathies (cat scratch disease, *Mycobacterium tuberculosis*, parasitic infections [*Toxoplasma gondii*], fungal infections [*Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides immitis*], and opportunistic infections] and non-infectious diseases (Kawasaki disease, sarcoidosis disease, etc.) are among differential diagnoses [4-6].

Primary and secondary skin lesions are seen in almost 35-43% of patients with tularemia. Although papules and vesicopapular lesions are the most common form of skin lesions, other skin lesions such as maculopapular or vesiculopapular rash, erythema nodosum, erythema multiforme, pustules, acneiform lesions, and urticaria also develop. Syrjala et al. reported that erythema nodosum was seen in 28% and erythema multiforme in 9% of the patients [7]. Skin lesions manifest in the second week and continue for about six weeks.

Tularemia diagnosis is based on characteristic disease history, physical examination and laboratory findings. Since oropharyngeal tularemia does not have specific clinical or laboratory findings, it is frequently recognized in endemic areas. Identification of bacteria with culture is the gold standard diagnostic test in tularemia diagnosis. *F. tularensis* can be isolated in the early period. Therefore, getting samples in suspected cases is very important. Since microbiological culture of *F. tularensis* requires a biosecurity level 3 laboratory and experienced personnel, demonstration of bacteria-specific gene sequences with polymerase chain reaction can be used instead.

However, serological tests have been the most frequently used method in the diagnosis of tularemia for around a century. Looking for antibodies against *F. tularensis* in tube

or group agglutination tests is the easiest diagnosis method. Microagglutination test (MAT) is the most frequently used method. For serological diagnosis of *F. tularensis*, World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) defines four-fold titer increase in agglutination tests as a sign of acute disease [8,9]. In seroprevalence studies, titers equal to or above 1:20 is considered significant [10]. Diagnosis is possible if the tube agglutination test shows a positivity at ≥ 160 titer in one sample, presence of symptoms and lack of vaccination history [10].

Tularemia is endemic in our country and in this region. Based on the fact that tularemia is epidemic in this region and on our experience with similar cases, tularemia was suspected in our patient. We reached the diagnosis with physical examination findings and microagglutination test positivity. The main treatment of tularemia is streptomycin. We used streptomycin in our patient, but ciprofloxacin was added to treatment due to lymph node suppuration. The patient responded to medical treatment favorably.

In conclusion, dermatologists, plastic surgeons should be aware that erythema multiforme and nodosum may be seen as the skin manifestations of tularemia and consider tularemia among differential diagnosis in endemic areas of the northern hemisphere.

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