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CLINICAL STUDY

MANAGEMENT OF CERVICAL LYMPHADENOPATHY IN PATIENTS WITH TULAREMIA

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SUMMARY

Purpose: To report the efficacy of lymph node drainage and oral ciprofloxacin treatment in tularemia patients with suppurative cervical lymphadenitis.

Materials and Methods: The study included 14 patients with cervical lymphadenitis or abscess caused by tularemia. All the patients were diagnosed by the help of the microagglutination test. All of the patients were treated using oral antibiotics, and drainage of the suppurative lymph node. Oral quinolones were used instead of parenteal streptomycin or gentamycin which have more side effects such as ototoxicty. All of the patients in the present study were followed-up on an outpatient basis.

Results: 10 out of 14 patients were healed following oral ciprofloxacin or doxycycline treatment, and proper lymph node drainage. Prompt drainage of abscess reduced the need of intravenous antibiotic usage and surgical excision of the lymph node.

In all, 4 of the patients underwent surgical removal of infected lymph nodes that resistant to medical treatment and drainage.

Conclusion: Careful out-patient follow up with regular drainage and proper antibiotic therapy reduces hospitalization need and invasive surgical intervention rate.

Keywords: Tularemia, cervical lymphadenitis, ciprofloxacin, surgery, puncture

TULAREMIYE BAĞLI SERVİKAL LENFADENOPATİ TANISI ALMIŞ HASTALARDA TEDAVİ YÖNETİMİ

ÖZET

Amaç: Tularemiye bağlı süpüratif servikal lenfadenit olgularında drenaj ve oral siprofloksasin tedavisinin etkinliğini saptamak.

Materyal Metod: Çalışmamızda tularemiye bağlı servikal lenfadeniti veya apsesi olan kliniğimize başvurmuş 14 olgu ele alınmıştır. Tüm hastaların tularemi tanısı hemaglütinasyon testi ile serolojik olarak doğrulanmıştır. Tüm hastalara süpüratif lenf nodunun drenajı yapılmış ve oral antibiyotik tedavisi verilmiştir. Aminoglikozidlerin ototoksisite gibi olası yan etkilerinden kaçınmak amacı ile tüm hastalara oral siprofloksasin veya doksisiklin verilerek polikliniğimizde ayaktan takip edilmiştir.

Bulgular: 14 hastadan 10'unda oral siprofloksasin veya doksisiklin tedavisi ile birlikte uygulanan drenaj ve takip neticesinde klinik olarak düzelmiştir.Medikal tedavi ve düzenli drenaja rağmen kliniği düzelmeyen 4 hastada enfekte lenf nodunun cerrahi olarak eksize edilmesi gerekmiştir.

Sonuç: Hastaların düzenli drenaj ve uygun antibiyotik tedavisi ile ayaktan izlenmesi cerrahi girişi gerekliliğini ve hospitalizasyonu azaltmaktadır.

Anahtar Sözcükler: Tularemi, servikal lenfadenit, siprofloksasin, cerrahi, ponksiyon

INTRODUCTION

Tularemia is a zoonotic bacterial infection caused by Francisella tularensis. There are several clinical types of tularemia: ulceroglandular, glandular, oropharyngeal, oculoglandular, typhoidal, and pneumonic. Ulceroglandular is the most common type of tularemia. Ulceroglandular and glandular types affect primarily the head and neck region[1]. As F. tularensis is an extremely virulent organism that is difficult to culture on standard media, in most cases laboratory diagnosis is based on serological assays, such as microagglutination or ELISA tests[2].Tularemia is a rare disease so that it is not frequently considered in the differential diagnosis of neck masses.[3,4].

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If a patient with cervical lymphadenitis does not show any clinical improvement despite the use of beta lactam antibiotics, tularemia must be investigated.

The suspected diagnosis is confirmed on the basis of serological testing[2]. Streptomycin and gentamycin are the antibiotic of choice for the treatment. F. tularensis is resistant to macrolides, co-trimoxazole, and beta-lactams, and in such cases aminoglycosides, tetracycline, or quinolones should be used[5]. In this paper we want to discuss the role of surgical drainage in the management of cervical lymphadenitis due to tularemia.Also we suggest out patient follow up with oral quinolones instead of parenteral streptomycin and gentamycin which have more side effects such as ototoxicity.

MATERIAL and METHODS

The study was conducted at Hacettepe University Hospital, Ankara, Turkey, a tertiary referral center in central Anatolia. The study included 14 patients that presented between 2011 and 2013 with a cervical neck mass because of tularemia by clinicians in the department of otorhinolaryngology. 8 of the patients were male and the 6 of them were female. The age range was 4-62 years (mean: 37 years).

The differential diagnosis of each neck mass was made initially based on history, physical examination, detailed endoscopic examination of the upper aerodigestive tract, and ultrasonographic imaging of the cervical mass. Cervical mass inflammationincluding hyperemia and tendernesswas the first symptom in each case. Malignancy originating from the head and neck region was also ruled out by detailed endoscopic examination of head and neck, as well as with CT or MRI. Patients with suspected tularemia underwent the microagglutination test performed at the National Tularemia Reference Laboratory of Refik Saydam Hygiene Center, Ankara, Turkey. Titers >1/160 were accepted as positive for tularemia. Following definitive diagnosis, the patients were given antibiotic treatment and referred to the department of infectious diseases for systemic examination.

RESULTS

All 14 patients presented with a neck mass due to tularemia.History showed that the rapidly growing mass in the upper neck of each patient first appeared <4 weeks before presentation, and that each patient had used oral antibiotics (most commonly amoxicillin-clavulanate and ampicillin-sulbactam). Due to the lack of response to antibiotic therapy given for tonsillitis, lymphadenitis, or neck abscess, 6 of the patients were referred to our clinic for further investigation. In 4 patients a water-borne infection was suspected based on anamnesis. None of the patients had a history of contact with animals. 2 of the patients had the oculoglandular type of tularemia, whereas the 12 others had the oropharyngeal type.

On physical examination the most commonly observed enlarged fluctuating suppurative lymph node was in the upper jugular lymph node group at level II. Accompanying symptoms were sore throat and tonsillitis in the patients with oropharyngeal tularemia, and parotitis and conjunctivitis in those with the oculoglandular type. Following serological verification of tularemia, oral ciprofloxacin was started in all the patients, except a 4-year-old boy who was given doxycycline.

Suppurative lymph nodes which requires drainage were diagnosed as fluctuant and tender masses in subdermal tissue. Inflammatory characteristics that include heat, pain, swelling, and redness were obvious.Drainage of the suppurative lymph node via incision or puncture was performed initially. Ciprofloxacin was prescribed in 750-mg tablet form b.i.d. All patients were followed-up regularly for 6 weeks, daily at first week.

Each patient received a 6-week course of antibiotic treatment, even those whose neck mass disappeared following drainage. In 4 (28.6%) of the patients the neck mass did not disappear after 6 weeks of antibiotic treatment, and excision of the enlarged inflamed lymph node was performed under general anesthesia. Following excision, the neck mass did not recur in any of those 4 patients. All 14 patients were healed without any complications with out-patient follow up and oral antibiotherapy. The patients' characteristics and results are shown in Table 1.

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Table 1. Patient characteristics and treatment options.

Patient number	Age	Sex	Disease type	Drainage	Antibiotic	Duration of antibiotic treatment (weeks)	Lymph node excision
1	56	F	Ulceroglandular	yes	Ciprofloxacin	6	yes
2	4	M	Oropharyngeal	yes	Doxycycline	3	no
3	28	M	Ulceroglandular	yes	Ciprofloxacin	6	no
4	24	M	Oropharyngeal	yes	Ciprofloxacin	6	yes
5	36	F	Oropharyngeal	yes	Ciprofloxacin	6	yes
6	14	M	Oropharyngeal	yes	Ciprofloxacin	6	no
7	62	M	Oropharyngeal	yes	Ciprofloxacin	6	no
8	51	M	Oropharyngeal	yes	Ciprofloxacin	6	no
9	42	F	Oropharyngeal	yes	Ciprofloxacin	3	no
10	48	M	Oropharyngeal	yes	Ciprofloxacin	6	no
11	34	M	Oropharyngeal	yes	Ciprofloxacin	6	no
12	39	M	Oropharyngeal	yes	Ciprofloxacin	6	no
13	44	F	Oropharyngeal	yes	Ciprofloxacin	6	no
14	37	F	Oropharyngeal	yes	Ciprofloxacin	6	yes

DISCUSSION

Tularemia is an acute zoonotic bacterial infection caused by F. tularensisan aerobic, non-capsulated gram-negative coccobacillus. F. tularensis can be transmitted to humans via tick bites, contaminated water, handling infected materials, and inhalation[1,4]. The incubation period is usually 3-5 days, but may vary from 1 to 21 days, and symptoms vary based on the mode of infection.The F. tularensis subsp. holarctica, which is a less virulent organism, primarily causes oropharyngeal infection, especially in Europe and Turkey[6]. F. tularensis subsp. tularensis generally causes the ulceroglandular type of tularemia[3]. The primary mode of transmission of F. tularensis in Turkey is thought to be via untreated spring water and consumption of contaminated food.

The clinical manifestations of tularemia range from asymptomatic illness to septic shock and death. Tularemia can present as otorhinolaryngological disease. Ulceroglandular, glandular, and oropharyngeal types of tularemia can occur in otolaryngologic patients, frequently causing diagnostic difficulty. Tularemia outbreaks due to contaminated water usually occur in fall and winter. Culturing and isolating the bacteria are difficult; as such, serological tests are required for definitive diagnosis. Tularemia should be considered in the differential diagnosis of patients with fever, pharyngitis or tonsillitis, and/or cervical lymphadenopathy that have not responded to beta-lactam antibiotics[7,8]. Although tularemia is not a common disesase in Western and European countries but it mut be suspected in cervical lymphadenopathy followed by an upper respiratory infection which is resistant to antibiotics such as penicillins Clinical suspicion and awareness of tularemia during the differential diagnosis of neck masses prevents

delayed diagnosis.Cervical tularemia may mimic other diseases, including bacterial abscesses caused by other bacterial infections, tuberculosis, brucellosis, or cat scratch disease. Chronic granulomatous inflammation caused by tularemia, especially in the chronic state, mimics tuberculosis, another common disease that causes cervical lymphadenopathy.

To avoid misdiagnosis serological testing must be performed. For agglutinins specific to F. tularensis the microagglutination test is the serological test of choice[2]. Early diagnosis and treatment of tularemia are necessary to avoid unnecessary etiological investigations and to prevent complications. First-line treatment of tularemia is antibiotherapy and/or surgery. Streptomycin and gentamycin are reported to be the antibiotics of choice for treatment of tularemia[1,9,10]

Ciprofloxacin inhibits DNA gyrase, thus is a bactericidal antibiotic. Oral fluoroquinolones could be an acceptable alternative to intravenous aminoglycosides or tetracyclines. Otolaryngologists must be aware of the ototoxic effects of aminoglycosides. Patient compliance with treatment is better with oral quinolones than with a long course of tetracyclines or aminoglycosides. Doxycycline is an antibiotic that has a bacteriostatic effect and inhibits protein biosynthesis on the ribosomal level. It can be used in pediatric patients as an alternative to aminoglycosides and quinolones[5]. Quinolones have bactericidal effects against F. tularensis and given their intracellular activity, are theoretically highly effective in the treatment of tularemia. The duration of antibiotic treatment is based on the clinical course of the disease. In the present study oral ciprofloxacin treatment was given for 6 weeks. Although gentamycin is among the most commonly used antibiotics, we didn't prescribe gentamycin because of its ototoxic effects.Snowden et al. performed surgical drainage in seven pediatric patients out of thirty cases and they used intravenous gentamycin as antibiotic.They did not report any side effect due to gentamycin.[9].

The optimal treatment of lymphadenopathy that is resistant to antibiotics is unclear; the literature is devoid of any relevant large-scale series or studies. Repetitive puncture, incision, and drainage, or excision are the most commonly reported treatment alternatives. Kızıl et al. suggested superselective neck dissection in suppurative lymph node cases unresponsive to antibiotics[1]. Garca et al. followed-up 12 patients that developed abscesses using repeated puncture in addition to medical treatment, but didn't perform surgical excision in any patient[11]. Some studies about treatment options in cervical lymphadenitis due to tularemia are summarized in Table 2.

Table 2. The treatment of cervical lymph node involvement in patients with tularemia, according to the literature.

	Number of patients	Need for drainage (n)	Antibiotic choice	Need for L.N excision (n)
Kızıl et al. (2012)	19	6	ciprofloxacin, streptomycin, doxycycline	5
Kaya et al. (2012)	23	4	ciprofloxacin, streptomycin, gentamycin	0
Çağlı et al. (2011)	25	23	ciprofloxacin, streptomycin, doxycycline, gentamycin	2
Snowden et al. (2011)	30	7	gentamycin, doxycycline	0
Garca et al. (2009)	8	3	ciprofloxacin, erythromycin	0

We advise puncture and drainage in cases of fluctuating large abscesses and infections with accompanying antibiotic treatment. Since it is not possible to take cultures unless there is a fluctant collection to be punctured,a majority of the cases received empirical antibiotic treatments especially beta lactams. This prevents early recognition and treatment of the tularemia. Serological tests which are investigated in blood must be ordered in case of clinical suspicion.

According to the literature, lymph node excision is required in cases of a fluctuant abscess or a large lymphadenopathy[1,10]. However, excision in such cases is difficult, because inflamed tissues are adhesive and hemorrhagic. Due to the complex anatomic structures of the neck, the potential complications of surgery must be considered. Cosmetic problems and scar formation commonly occur after surgery because of the chronic granulomatous infectious nature of the disease; as such, excision of lymph nodes wasn't considered a first-line treatment option in the present study. Instead, appropriate and careful antibiotic treatment, and repetitive drainage accelerated the healing process. Only 4 of the present study's 14 patients required excision following antibiotic treatment and drainage. Oral quinolones were used instead of parenteal streptomycin or gentamycin which have more side effects. Prompt drainage of abscess and removal of the infection site may reduce the need of intravenous antibiotic usage and surgery. Since ototoxicity is a unforeseen side effect especially in children we avoid to use these antibiotics.

All of the patients in the present study were followed-up on an outpatient basis. Long-course antibiotic therapy and meticulous follow-up including drainage may reduce the need for lymph node excision or neck dissection in patients with tularemia.

CONCLUSION

Based on the clinical outcome in the 14 presented patients, we recommend long-term oral ciprofloxacin therapy, together with repetitive aspiration and drainage, instead of urgent lymph node excision or neck dissection, for the treatment of cervical lymphadenitis due to tularemia.

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