

Diagnostic challenges in cervical tuberculous lymphadenitis: A review

Hande Senem Deveci,¹ Mustafa Kule,² Zeynep Altin Kule,² Tulay Erden Habesoglu¹

¹Department of Ear, Nose and Throat, Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey

²Department of Ear, Nose and Throat, Mugla State Hospital, Mugla, Turkey

ABSTRACT

Tuberculosis is a very serious disease and incidence is once again on the rise. Lymph node tuberculosis is one of the most common extrapulmonary manifestations of tuberculosis. In differential diagnosis of chronic, painless cervical lymphadenopathy, cervical tuberculous lymphadenitis should be kept in mind. A high index of suspicion is needed for diagnosis of tuberculous lymphadenitis, which is known to mimic a number of pathological conditions. This article reviews epidemiology, clinical manifestations, and diagnostic techniques for cervical tuberculous lymphadenitis.

Keywords: Cervical tuberculous lymphadenitis; extrapulmonary tuberculosis; tuberculosis.

Tuberculosis (TB) is a common, and in many cases lethal, infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis* [1]. Today in developing countries tuberculosis is still a major health problem. As a consequence of increased human immunodeficiency virus (HIV) prevalence and increasing immigration rate, tuberculosis (TB) is also re-emerging as a health care problem in developed countries [2]. Tuberculosis which mainly involves the lungs can also cause infection in almost all other organs and tissues in the body. TB bacilli enter the lymphatic system and blood stream to reach the extrapulmonary organs. Notable extrapulmonary infection sites include the pleura, the central nervous system, the lymphatic system, the genitourinary system, and the bones and joints [3]. Lymph node tuberculosis (LNT) is

a common cause of lymphadenopathy in areas in which TB is endemic. In countries with a low prevalence of TB, LNT is the most common extrapulmonary form [4]. In contrast, in high prevalence areas, the LNT incidence is second to that of TB pleuritis [2]. The most common LNT form is mycobacterial cervical lymphadenitis (MCL) [5, 6]. Although new diagnostic methods have been developed, especially in patients without a history of tuberculosis, the cervical tuberculous lymphadenitis (CTL) diagnosis is still elusive. In differential diagnosis of CTL, other granulomatous lymphadenitis should be considered such as non-tuberculous mycobacteria (including *M. scrofulaceum*, *M. avium*, and *M. haemophilum*), sarcoidosis, toxoplasmosis, tularemia, fungal disease, cat-scratch disease and neoplasms [7, 8]. The diagnosis is necessitating a high index of suspicion.

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Correspondence: Dr. Hande Senem DEVECİ. Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi, Kulak Burun Bogaz Klinigi, Istanbul, Turkey.

Tel: +90 216 - 578 30 00 e-mail: senemesen@yahoo.com

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Kent and et.al. alleged that CTL is the result of lympho-hematogenous spread of pulmonary tuberculosis [9]. According to Powell, this entity is a hyperreaction of lymph nodes against previous pulmonary tuberculosis [10]. And also Yew et al. suggested that the predominant pathway of spread of the tubercle bacilli to the cervical lymph nodes is from lung parenchyma as the lymphatics of the right lung and the lower lobe of the left lung normally drain to the right supraclavicular lymph nodes and then upwards to the right lower cervical chain [11]. However, the pathogenesis of CTL without pulmonary tuberculosis cannot be explained by this theory, and also alternate routes of spread to lymph nodes, such as the tonsils and adenoids, have been proposed [12]. Lymph node tuberculosis could be also occurring by direct exposure to infection [3].

In this review, we aimed to discuss the diagnostic methods of CTL and to evaluate the usefulness of these diagnostic methods.

Dermographic findings

Age and gender distribution of CTL is different from the pulmonary tuberculosis. CTL is more frequent in females and in the younger age groups, whereas pulmonary tuberculosis is more common in males and in the older age groups [2, 13, 14]. Dandapat et al. have suggested that this phenomenon occurs as a consequence of male-dominated communities, where women experience poorer living conditions, and because young females generally notice differences in their appearance earlier than males [15].

Clinical presentation

In the differential diagnosis of a cervical mass, CTL should be kept in mind especially in endemic areas. CTL may present as a unilateral single or multiple painless lump, mostly located in the posterior cervical or supraclavicular region [6, 16]. The duration of lymphadenopathy at time of presentation is typically 1–2 months, varying from 3 weeks to 8 months [8, 17]. Fistula formation can be seen in almost 10% of the mycobacterial cervical lymphadenitis [6, 18], though it is rare in atypical cases [19]. There is a significant variability in the literature on the occurrence of clinical signs and symptoms of LNT other than the cervical mass. However night sweats,

weakness, cough and fever could be also seen in these patients in different ratios [2, 15]. These systemic symptoms are more commonly seen in HIV positive patients [20].

Also in HIV-positive patients the lymphadenopathies are more commonly seen as symmetrical and multiple contrasted with presentation with focal and asymmetrical lymphadenopathies of HIV-negative patients [21].

Accompanying pulmonary tuberculosis is reported in 18%–42% of patients. The higher rate of pulmonary tuberculosis is seen in HIV-positive patients rather than HIV-negative patients [22].

Diagnostic tools

In order to make a diagnosis of CTL suspicion is mandatory. A detailed history and physical examination which is supported with hematological tests, tuberculin test, imaging techniques, fine-needle aspiration (FNA), and molecular tests will help arrive at an early diagnosis of tuberculous lymphadenitis and allow early initiation of treatment before the final diagnosis can be made by incisional biopsy and culture [8, 23, 24].

Hematological tests

Although there is no specific blood test, leukocytosis, thrombocytosis, anemia, hyponatremia and increased ALP results are associated with chronic disease condition and these results create a doubt about an infective condition. Also elevated ESR show up a non-specific inflammatory response [25, 26].

Extrapulmonary involvement can be seen in more than 50% of patients with concurrent AIDS and pulmonary tuberculosis [3]. Because of the coinfection risk of extrapulmonary forms of tuberculosis in HIV-positive patients, all patients with CTL suspects have to be tested for HIV [14, 26, 27].

Tuberculin skin test

Tuberculin skin test (TST) is used to show delayed-type hypersensitivity reactions against mycobacterial antigen, in which the reagent is mostly protein purified derivative (PPD). The test becomes positive 2–10 weeks after the mycobacterial infection. Positive reactions (>10-mm induration) can occur in *M. tuberculosis* infections. Suspicious reac-

tions (5- to 9-mm induration) can occur after BCG vaccination, *M. tuberculosis* infection or nontuberculous mycobacterial infections. Negative reactions (<4-mm induration) represent a lack of tuberculin sensitization. False-negative reactions can occur in at least 20% of all people with active tuberculosis. The test may also be false positive in different conditions, like other infections, metabolic disease, malnutrition, live virus vaccination, malignancy, immunosuppressive drugs, newborns, elderly people, stress, sarcoidosis and inadequate test application [28]. Mandatory Bacille Calmette–Guerin (BCG) vaccination is in some countries may increase the false-positivity [2].

Although the value of the test is controversial [29], the positivity of TST is up to 98% in USA [17] and 100% in Turkey [30] in HIV-negative tuberculosis patients. Thus TST is a valuable, but non-specific test for assessment of TB in Turkey [2, 30].

Imaging techniques

Chest X-ray, neck ultrasound (USG), computerized tomography (CT) and magnetic resonance imaging (MRI) of neck can be performed in cervical lymphadenopathies.

Chest X-ray findings may be positive in 10–40% of patients [31]. However, the normal chest X-ray should not exclude the CTL diagnosis.

The changes in size, shape (L/T ratio), echogenicity and morphology of the nodal hilum or cortex have been suggested as sonographic criteria for differentiation of benign pathologies from malignant. However, USG findings do not show disease-specific features for CTL. It can also be used as an imaging tool for the guided aspirations. Therefore, when combined with fine-needle aspiration, it has a very high sensitivity and specificity [32].

CT and MRI are valuable complementary techniques in evaluation of CTL. However, they are not sufficient to make a certain diagnosis. They accurately demonstrate the sites, pattern and extend of the disease. Imaging features are varied and non-specific, although rim enhancement or calcification, if present, can be a strong indicator of the disease [33]. There are three patterns of nodal involvement in tuberculosis lymphadenitis on CT or MR images [34, 35]. In the early course of disease, the nodes are homogenous in attenuation and after adminis-

tration of intravenous contrast they enhance homogeneously. As the disease progress, the second and the most common pattern, a node with central area of necrosis, is seen. At CT, the affected nodes have center of low attenuation with an enhancing rim. At MRI, the enhancing areas are of intermediate signal intensity with T1-weighted sequences and are hypointense with T2-weighted sequences, whereas non-enhancing areas are relatively hypointense with T1-weighted sequences and markedly hyperintense with T2-weighted sequences. The non-enhancing areas indicate caseation or liquefaction necrosis, and the enhancing areas indicate granulation tissue with an inflammatory hypervascularity and increased vascular permeability. The third pattern is a fibrocalcified node that is usually seen in patients who have been treated. At CT, the node is homogenous and the calcification could be noticed. At MRI, it is homogeneously hypointense both in T1- and T2-weighted sequences and does not enhance after injection of contrast material [33, 34].

Fine-needle aspiration

In fine-needle aspiration (FNA), a thin needle is inserted into an infected, swollen, superficial lymph node. Then, the taken aspirate material could be allocated for cytological examination, acid-fast bacilli (AFB) staining, culturing and/or molecular testing.

Fine-needle aspiration cytology shows up a well-formed epithelioid granuloma and the presence of caseous necrosis [36]. These finding are highly suggestive of tubercular etiology, especially in developing countries where the incidence of tuberculosis is high [36]. The sensitivity and specificity of FNA cytology in the diagnosis of tuberculous lymphadenitis are 88% and 96%, respectively [37]. However, typical granulomas and caseation are less likely to be found in HIV-positive tuberculosis lymphadenitis because of the impaired T-cell function [20]. Therefore bacteriological confirmation is essential. Combination of FNA cytology with the culture or a TST further increases the diagnostic yield in CTL [29, 38].

FNA material also subjected to Ziehl-Neelsen (ZN) staining for AFB, mycobacterial culture and molecular test [20].

ZN staining and microscopic evaluation is rapid, cheap and easy. Sensitivity ranges from 46–78%

and the specificity is actually 100% [36]. But the sensitivity ratio varies according to the source of the sample. Tandesse et al. revealed that concentrated aspirate material increase the yield of AFB staining procedure [39].

Culture

A definitive diagnosis of tuberculosis lymphadenitis can be made by demonstration of *M. tuberculosis* in an affected lymph node by culture. However, a negative culture result should not exclude the diagnosis of CTL [28]. Isolation of mycobacterium by culture is possible in 10–69% of the cases [6, 24, 40]. And also the long duration of culture (6–8 weeks) cause delay in initiation of treatment and is assessed as time-consuming.

Molecular testing

Polymerase chain reaction (PCR) which is a nucleic acid amplification test, provide a rapid, specific and sensitive diagnosis of *M. tuberculosis*. [24]. After FNAs, PCR should be performed for the samples. When we scan the literature, the positivity of PCR from FNA materials were found 71.4%, 76.4% and 92.1% in three different studies [41, 42]. In one of these studies, Suzuki K. et al. compared the sensitivity of cytological examination, smears, cultures and PCR technique using an aspiration procedure for cervical tuberculous lymphadenitis. And the ratios of these techniques were 13.3%, 50%, 60% and 71.4%, respectively [43].

Histopathologic examination and PCR of an excisional biopsy should be recommended only for patients in whom FNA-PCR is negative or when there is discrepancy with the clinical impression [24].

Histopathology

Histopathologic examination is one of the most important diagnostic method of CTL [6, 44, 45, 46]. Langerhans giant cells, caseating necrosis, granulomatous inflammation and calcification can be seen in histopathological examination [47]. Though histopathology is most reliable method for diagnosis of cervical lymphadenitis, its feasibility is limited due to its non-acceptability, as it is an invasive procedure [20]. Although it's an invasive technique, early surgical excision of the tuberculous

lymphadenitis is considered as an adjunct to anti-biotic therapy. So surgical excision has been recommended for treatment failure cases of tuberculosis lymphadenitis and for patients who have discomfort from tense, fluctuant lymph nodes [17, 31]. Preferred surgical method is excision of an infected lymph node. Because incisional biopsy is associated with sinus tract and fistula formation and therefore is contraindicated [48].

Conclusion

Tuberculosis (TB) is a major health concern in developing countries. This disease is a systemic disease which may give rise to cervical lymphadenitis as an extrapulmonary manifestation of the disease. The most usual signs and symptoms are the appearance of a chronic, painless mass in the neck, which is persistent and usually grows with time. Because of no other remarkable symptom their diagnosis and distinction need a high index of suspicion, and application of a variety of diagnostic modalities. However, it is not possible or practical to apply all of the diagnostic procedures in all patients. This would be time consuming and expensive. Increased ESR, leukocytosis thrombocytosis, anemia, hyponatremia and increased ALP results put forward a non-specific inflammation or a chronic disease status. Chest radiographs do not have any diagnostic value. And tuberculin skin test is also not valuable in areas where BCG vaccination is mandatory. CT and MRI scans may show characteristic signs and the localization of the CTL which may help if the surgical excision would be planned in future. After a FNA, a combination of conventional techniques (such as cytology, staining, culture) with PCR must be applied for the rapid and early diagnosis of CTL. Therefore, the value of FNA is indisputable. The definitive diagnosis of tuberculous lymphadenitis is done by excisional biopsy and histopathologic examination if all other techniques fail.

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