

# Tuberculous Lymphadenitis is a Generalized Disease (A Review of 21 Cases)

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## Abstract

**Objective:** Tuberculous lymphadenitis (TL) is the most frequent presentation of extrapulmonary tuberculosis. The purpose of this study is to review many aspects of the patients with TL, and to determine whether TL is a generalized disease.

**Methods:** The files of the cases diagnosed over a period of 20 months in our hospital were reviewed clinically, radiologically, pathologically, and regarding treatment and outcome. The diagnosis has been established by the presence of caseating granulomas or bacteriologic confirmation by smear or culture, and a clinical diagnosis of tuberculosis (TB) with response to specific antituberculous therapy. Anatomic distribution of involved lymph nodes, extrapulmonary involvement other than lymphadenitis, and pulmonary TB have also been assessed during the diagnostic work-up for TL.

**Results:** Mean age was  $34.4 \pm 14.2$ , 16 patients were female, 5 were male. In 15 (71.4%) of the cases, lymphadenitis was

determined in only one location, and in 6 (28.6%) in more than one location. Pulmonary tuberculosis was detected in 9 (42.9%) of the cases while other extrapulmonary tuberculosis was detected in 5 (23.8%) of the cases (two cases of cutaneous, two of peritoneal, and one of colonic TB).

In 14 (66.7%) of the cases there was either generalized lymphadenitis or localized lymph node involvement together with pulmonary tuberculosis or other extrapulmonary tuberculosis. TL in a single location was detected in 7 (33.3%) patients with no pulmonary or extrapulmonary tuberculosis. Concerning the number of patients with TL, no significant difference was found between localized and generalized involvement ( $p=0.397$ ).

**Conclusion:** Our data, though not statistically significant, suggest that TL is not a localized disease.

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**Key words:** Tuberculous lymphadenitis, extrapulmonary tuberculosis.

## Introduction

Tuberculosis (TB) is one of the most important notifiable diseases in developing countries, and the most important one in Turkey. Tuberculous lymphadenitis (TL) is the most frequent presentation of extrapulmonary TB. The history and clinical features vary considerably among patients, and problems may arise not only in diagnosis but also in treatment (1-4).

The clinical incidence of human TB has decreased as a result of effective chemotherapy. On the other hand, in the underdeveloped or developing countries, the incidence of extrapulmonary TB or lymphadenopathy associated with TB has remained constant or increased. In the USA the proportion of all reported cases of extrapulmonary TB has risen from 8% in 1964 to 15% in 1981 and 17.5% in 1986 (5,6). The same trends have been observed in Hong Kong, where the total TB notification rates have decreased from 404 (per 100000) in 1960 to 254 in 1970 and 112 in 1990. The proportion of nonrespiratory cases, however, has increased from 1.2% in 1967 to 6.6% in 1990 (7).

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Today, *M. tuberculosis* kills 2.9 million people each year, probably more than any other single infectious pathogen. TB primarily affects adults in their most productive years. Among the reasons for the increasing number of TB cases throughout the world, the growing epidemic of human immunodeficiency virus (HIV) infection is the most important. HIV appears to be a potent facilitator of TB. With the spread of HIV infection, the number of TB cases has increased significantly in many African countries and in certain populations in Asia, Europe, and North and South America (8).

This study was aimed at reviewing the clinical features and management of TL regarding various clinical presentations, presence of generalized disease and problems in treatment.

## Methods

All patients enrolled in the study have been admitted to the Atatürk Chest Diseases and Surgery Center, Ankara, Turkey. The adult cases with TL who have been presented between March 1996-November 1997 were retrospectively assessed.

The diagnosis of TL has been confirmed either by the presence of caseating granuloma in a lymph node biopsy sample, or an acid-fast bacilli positive smear or culture of lymph node specimen.

A detailed medical history has been taken, and a thorough physical examination was performed in each case. Chest radiographs from all patients were assessed on admission and subsequent follow up.

All enrolled patients have had sputum, gastric lavage, or bronchial lavage samples were examined for acid-fast bacilli by smear and culture on Löwenstein-Jensen media.

Anatomic distribution and pulmonary TB have also been assessed during the diagnostic work-up for TL. The patients have been followed up closely for their response to antituberculous treatment.

The chi-square test was used to assess the significance of difference between the incidences of generalized and localized lymph node involvements.

## Results

During the study period, approximately 2000 patients have been treated for TB at our center, and of these only 21 (1%) had TL. There were 16 females and 5 males in

the present series. The mean age was  $34.4 \pm 14.2$  (range 17-60 years).

All patients had one or more systemic symptoms, most commonly malaise, sweating, fever, weight loss (Table 1) and chest symptoms. HIV infection was not demonstrated by ELISA in any of the 21 patients.

Symptom	Number of patients	%
Malaise	13	61.9
Fever	5	23.8
Weight loss	8	38.1
Sweating	9	42.8
Total	21	100

There was a previous family history of TB in six patients. The chest radiographs in 16 patients showed various findings consistent with active or prior pulmonary TB or mediastinal widening (Table 2). Twelve patients have undergone thoracic computed tomography (CT), and three have undergone abdominal CT. In only two patients, thoracic CT scan was normal. In three patients hilar/mediastinal lymphadenopathies, in four patients infiltration and fibrosis in parenchyma, in one patient infiltration and cavitation, in one patient infiltration, cavitation and mediastinal lymphadenopathies, in one patient only axillary lymphadenopathy were detected (Table 3). In two patients, abdominal CT scan was normal, and in one with multiple cervical lymphadenopathies, diffuse abdominal calcified lymphadenopathies were detected (Figure 1).

The diagnosis of TL was made by biopsy or smear of lymph node aspirate. Bronchoscopy was performed in three patients. But transbronchial needle aspiration was not performed. Diagnostic methods in TL are summarized in Table 4. Histological features of TB were identified in 20 of 21 patients who had undergone lymph node biopsy. Fine needle aspiration was performed

Radiographic findings	Number of patients	%
Normal	5	23.8
Infiltration	3	14.3
Hilar enlargement	5	23.8
Hilar enlargement and infiltration	4	19.0
Cavitation	1	4.8
Diaphragmatic elevation	1	4.8
Mediastinal enlargement	2	9.5
Total	21	100

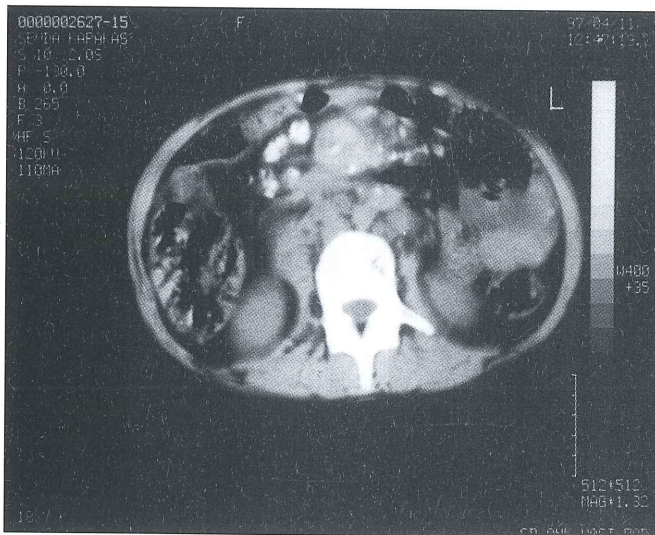


CT findings	Number of patients	%
Normal	2	16.6
Hilar/Mediastinal LNE	3	25
Infiltration and fibrotic changes	4	33.3
Cavitation+infiltration	1	5.3
Cavitation+infiltration+ Mediastinal LNE	1	8.3
Axillary LNE	1	8.3
<b>Total</b>	<b>12</b>	<b>100</b>

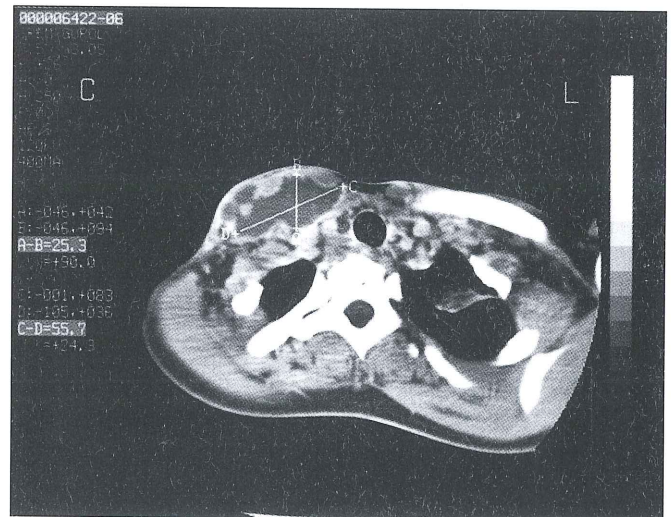
LNE: Lymph node enlargement

Diagnostic methods	Number of patients	%
Peripheral lymph node biopsy	17	80.9
Cervical	(8)	(38.1)
Axillar	(5)	(23.8)
Supraclavicular	(1)	(4.8)
Scalen	(1)	(4.8)
Submandibular	(1)	(4.8)
Submental	(1)	(4.8)
Mediastinoscopy	1	4.8
Thoracotomy	1	4.8
Laparoscopy	1	4.8
Fine needle aspiration*	1	4.8
<b>Total</b>	<b>21</b>	<b>100</b>

\*Bacteriological diagnosis of tuberculosis (smear and culture)



**Fig. 1.** Multiple calcified abdominal lymph nodes on CT scan



**Fig. 2.** Thoracic CT scan depicting paratracheal and supraclavicular lymphadenopathy forming abscess

from the supraclavicular lymph node in one case. The Ziehl-Neelsen-stained smear as well as culture of the aspirated specimen were positive for *M. tuberculosis*. This patient has already been being treated for pulmonary tuberculosis at the time of the diagnosis. She has presented with fluctuant supraclavicular swelling and a CT scan showed right supraclavicular and paratracheal lymph node enlargement (Figure 2).

In 15 patients (70.1%), lymphadenitis was in only one location, in 6 patients (28.6%) in more than one location. The sites of TL, and accompaniment of pulmonary and other extrapulmonary TB are summarized in Table 5. Pulmonary TB was seen in 9 (42.9%) of the cases. Of these 9, two had microbiological evidence of active pulmonary TB, and seven patients had radiographic abnormalities consistent with active disease. Other extrapulmonary TB was seen in 5 (23.8%) of 21 cases (two cases of cutaneous, two of peritoneal, and one of colonic TB). The diagnosis

has been verified by tissue biopsy in these five cases.

In 14 (66.7%) of the cases, there was either generalized or localized lymph node involvement together with pulmonary tuberculosis or other extrapulmonary tuberculosis. TL in only one location was detected in 7 (33.3%) patients without pulmonary or extrapulmonary tuberculosis. Concerning the number of patients with TL, no significant difference was found between localized and generalized involvement ( $p=0.397$ ).

Median treatment duration was  $7.33+5.85$  (range 3-24) months in 21 patients. Twelve patients were treated at least 6 months; in these patients median treatment duration was  $10.33+6.26$  months (range 6-24). Twenty of the cases given four antituberculous drugs (isoniazid, rifampin, pyrazinamide and ethambutol or streptomycin) were new cases of TL with/without pulmonary or extrapulmonary TB. Cure was observed in 12 patients. Five patients were lost to follow-up after the 3rd month of



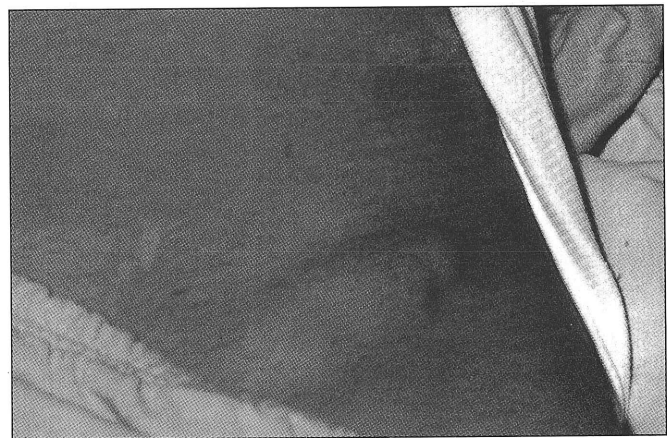
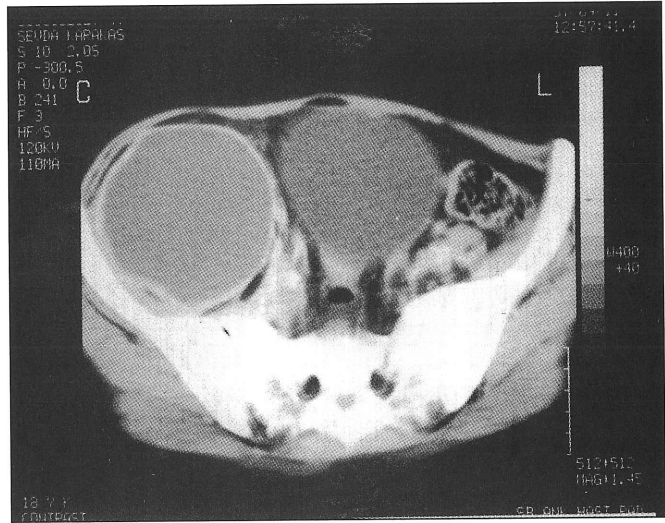
**Table 5. Anatomic distribution of involved lymph nodes and sites of accompanying pulmonary and extrapulmonary tuberculosis.**

Location	Tuberculous lymphadenitis		Extrapulmonary tuberculosis		Pulmonary tuberculosis	
	n	%	n	%	n	%
Cervical	10	47.6	2	9.5	4	19
Axillary	1	4.8	–	–	–	–
Mediastinal	3	14.3	–	–	1	4.8
Abdominal	1	4.8	1	4.8	–	–
Generalized	6	28.6	2	9.5	4	19
Total	21	100	5	23.8	9	42.8

antituberculous treatment. One patient with cutaneous TB was previously hospitalized for skin lesions, lymphadenopathy and miliary tuberculosis and after two months she herself had stopped her treatment. After taking biopsies (from lymphadenopathy, liver and skin) and verifying the diagnosis, antituberculous treatment was started again. Her lymphadenopathies diminished in size after 4 months of tuberculous treatment. In another patient, there were diffuse cervical lymphadenopathies with diffuse abdominal lymphadenopathies. In the third month of the antituberculous treatment, cervical lymphadenopathies became smaller but on the 6th month, abdominal lymphadenopathies formed a psoas abscess between the muscles and drained through the right inguinal region (Figure 3). The smear and culture of abscess specimen were negative for acid-fast bacilli. Antituberculous treatment was given for 12 months to this patient, and surgical drainage was performed. Six months later, the psoas abscess had recurred, and a second surgical drainage had been performed. The smear and culture of abscess material was again negative for acid-fast bacilli. The patient is still in follow-up without treatment. In one patient, supraclavicular lymphadenopathy had developed in the 6th month of her anti-tuberculous treatment for pulmonary TB (Figure 2). Rifampicin resistance was determined by culture of abscess specimen, and sputum has also revealed rifampicin resistance. Her treatment was continued with isoniazid, pyrazinamide, ethambutol. Four months later, her lymphadenopathy has regressed. Only one of the 21 cases, not among the above-mentioned 20 cases had multi-drug-resistant pulmonary TB with TL and tuberculous peritonitis. Re-treatment with ethambutol, ofloxacin, amikacin, ethionamide and roxithromycin has been given to this case for 24 months.

## Discussion

TL is seen in 3-5% of all TB cases. Ethnic group, age and sex are related with development of TL. It is most com-



**Fig. 3.** View on right inguinal region and psoas abscess on abdominal CT scan

monly seen in Asian people, blacks and females and between the ages 20 - 40. Female to male ratio is more than 2/1 (1-5). Patients infected with HIV have a higher risk of developing TB of all forms, particularly extrapulmonary involvements, which may occur in up to 70% of all HIV infected individuals who develop TB. Furthermore, HIV-infected persons who develop TB are relatively more likely to develop rapidly progressive disease, and certain extrapulmonary sites such as lymph nodes and meninges are more frequently affected in HIV-infected individuals compared with those not infected (1,6,9).

The mean age was 34.4 with a range of 17-60 years, while female to male ratio was 3.4/1 in our series. Our cases were 1% of all TB patients followed during the same period, in our hospital. This ratio is low because patients with TL are also followed on an outpatient basis in our hospital, or in otorhinolaryngology departments. TL is commonly seen in the head and neck region.



Anterior and posterior cervical, supraclavicular, submandibular, and rarely preauricular and submental regions are affected in an order of decreasing incidence. Less commonly, axillary, abdominal, mediastinal and hilar involvements can be seen in descending frequency, respectively. Generalized lymphadenitis is seen most rarely with a rate of 3% (1-5,10,11). Cervical involvement (47.6%) was the most common presentation, and generalized lymphadenitis was detected in 6 patients (28.6%) in our series.

The most common symptom is swelling of involved lymph nodes. Weight loss, fever, anorexia, weakness and pain are seen in less than 20% of the cases. Previous reports have emphasized the low incidence of systemic symptoms and changes in the chest radiograph (1-4). At least one systemic symptom was present in each of our cases. Radiological abnormalities are seen in less than 30% of adult patients with TL (11). Changes in chest radiographs consistent with either previous or active TB were identified in 76% of our cases, and 42.8% of the cases had also pulmonary TB.

The diagnosis of TL is made by biopsy, or smear or culture of lymph node specimen. Excisional biopsy is recommended by some authors to avoid complications (1-5). A definite diagnosis requires demonstration of *M. tuberculosis* in the pus from draining sinuses, or smear, culture or histology of lymph nodes. Acid-fast bacilli can be demonstrated in 25-50% of lymph node smears. The isolation rate on culture of biopsy or needle aspiration specimen is about 60-70%. This relatively low isolation rate probably reflects a very small population of organisms within the lymph nodes which become enlarged as a result of a hypersensitivity response to tuberculo-protein. Histologically, tuberculous lymphadenitis may show mild reactive hyperplasia or granuloma, usually with caseation and necrosis (12). In our study, the majority of the diagnoses were made histologically. In two patients, culture results of abundant lymph node and abscess specimens were negative for *M. tuberculosis*. In only one patient, smear and culture of supraclavicular lymph node aspiration specimen were positive.

Fine needle aspiration (FNA) used extensively in the diagnosis of mycobacterial lymphadenitis has become a first-line diagnostic technique. Combined use of FNA cytologic examination and Mantoux test has been efficient in the diagnosis of TL (13,14). However, absence of specific cytologic findings of granulomatous lymphadenitis, or negative acid-fast bacilli smears requires excisional biopsy or repeated FNA. The diagnostic efficacy of FNA cytology is quite variable with a 46% sen-

sitivity and a 90% specificity. With the advance of molecular diagnosis, various polymerase chain reaction (PCR) methods in diverse clinical specimens have been introduced for an easy and quick diagnosis of *M. tuberculosis*. The sensitivity of FNA cytology alone in diagnosing cervical TL is 52.9% and that of PCR is 76.4%. Combined FNA cytology with PCR has a sensitivity of 82.4% (15). Bronchoscopy has an important role in the diagnosis of intrathoracic TL and should be considered before other invasive procedures. Baran, et al. (16) reported a very high diagnostic yield by mucosal biopsy from the site of ulcerating granuloma and a 45% success rate by transbronchial or transcarinal aspiration in the presence of tracheal, carinal, or bronchial displacement by enlarged lymph nodes. Transbronchial needle aspiration is a useful and safe means of diagnosing the etiology of intrathoracic adenopathy in patients with HIV infection, particularly in those with mycobacterial disease. Transbronchial needle aspiration can also provide a rapid diagnosis of TB, and frequently provides the only diagnostic specimen in patients with HIV infection and mediastinal or hilar adenopathy (17,18).

The most characteristic CT finding of TL is the presence of low-density mediastinal and hilar lymph nodes in patients with AIDS, and in those HIV-seropositive without AIDS. Low-density mediastinal and/or hilar lymph nodes on CT, while not pathognomonic, is sufficiently characteristic for tuberculosis to warrant empirical anti-tuberculosis therapy pending results of the cultures (19). Our patients were not assessed regarding these aspects.

According to the WHO 1993 guidelines for TB treatment, short course chemotherapy regimens have been recommended (8). Treatment of TL for 6 months resulted in a relapse rate of 3.3%, with a mean follow-up of 31 months after completion of treatment. Treatment for 9 months resulted in a relapse rate of 2.7%, with a mean follow-up of 20 months (20). Despite the limitations of the literature, 6 months of therapy is probably sufficient for patients with TL. Most recent national and international treatment guidelines also recommend a treatment for 6 months. Excision of TL is not enough for treatment of TL. Antituberculous treatment must be given in adequate dosage for an adequate time in all types of extrapulmonary TB (1,8,20-22).

In 25% of cases with TL, lymph nodes may increase in size and new nodes may appear both during and after chemotherapy without indicating a failure of treatment or relaps (21,22). In the British study, existing lymph nodes increased in size in 12% of the patients and fresh lymph nodes appeared in another 12% within the first 8

months of chemotherapy. At the end of the chemotherapy, residual nodes were palpable in 9% of the patients, and new nodes appeared in 11%. These nodes were sterile on culture, and their enlargement or emergence might be due to hypersensitivity to tuberculo-protein released from disrupted macrophages and did not indicate an unfavourable outcome (21). In one of our patients, supraclavicular lymphadenopathy has occurred during treatment for pulmonary TB. Another patient has developed psoas abscess during treatment of TL.

With the advent of modern, effective antituberculosis chemotherapy, routine surgical excision or therapeutic aspiration of enlarged cervical lymph nodes was unnecessary (2), and indeed, has been shown to confer no advantage (21). Even for the nodes that enlarge after chemotherapy, operation is not necessarily indicated as the enlargement is usually transient. Surgery would be reserved for diagnostic biopsy and the unusual situation of persistent discharging abscess or sinuses (1,11,21).

Previous reports have emphasised the low incidence of systemic symptoms and changes in the chest radiograph (1-5). However, Pier, et al. (23), reported that TL is a generalized disease. In this study, in 35.5% of the TL cases, concurrent pulmonary TB was noted. In only seven of the patients, TL was seen in one region. The other patients had generalized TL, or another organ involvement with TB. For this reason, patients must be examined systemically.

In our series, all patients presented with systemic symptoms, high incidence of pulmonary tuberculosis (42.9%) and extrapulmonary tuberculosis (23.8%). The rates of generalized lymphadenitis (28.6%), pulmonary and other extrapulmonary TB together with TL (66.7%) were higher in our series. In 14 (66.7%) of the cases there was either generalized lymphadenitis or localized lymph node involvement together with pulmonary tuberculosis or other extrapulmonary tuberculosis. TL in a single location was detected in only 7 (33.3%) patients without pulmonary or extrapulmonary tuberculosis. However, concerning the number of patients with TL, no significant difference was found between localized and generalized involvement ( $p=0.397$ ).

In conclusion, our data has shown that TL is not a localized but a systemic disease.

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