INTRODUCTION

Tuberculosis (TB) is a major health concern in developing countries. Its association with low socioeconomic status is well established. Of the 22 highest burdened countries that account for 80% of the global TB cases, 17 are classified as low-income countries (1). The World Health Organization (WHO) estimates that 98% of the 3 million annual TB deaths and 95% of the 8.4 million new TB cases occur in developing countries (2). A consequence of increasing immigration and human immunodeficiency virus (HIV) prevalence, TB is also re-emerging as a health care problem in developed countries. However, recent data from the United States suggest that, in the incidence of TB, socioeconomic factors act independently of the HIV epidemic (3).

In practically all TB infections, regional lymph nodes are involved. TB bacilli enter the lymphatic system and bloodstream to reach the extrapulmonary organs. Lympho-hematogenous spread is limited by the immune system and more than 90% of infected people recover, as indicated by tuberculin skin test (TST) (4,5). Lymph node tuberculosis (LNT) occurs either by reactivation of dormant TB bacilli in lymph nodes or, very rarely, by direct exposure to infection (6).

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. In contrast, in high prevalence areas, the LNT incidence is second to that of TB pleuritis.

In Turkey, the National Reference Laboratory and Epidemiology Unit was established through cooperation with the Refik Saydam National Public Health Agency and Japan International Cooperation Agency in 1999, and soon afterward, more reliable data on TB epidemiology became available. Turkey is a country that has a moderate level of TB with an incidence of 26/100,000, and the incidence of LNT is lower than that of pleural TB according to a 2007 report of the agency. The incidence of pulmonary TB in Van and Izmir Provinces was reported to be 29 and 16.4 per 100,000, while the mortality rates for TB were found to be 0.6% and 4.6%, respectively. TB is responsible for 0.08% and 0.27% of all deaths in Van and Izmir, respectively. The incidence of extrapolmonary TB was found to be 30.7/100,000 in Izmir and 29.6/100,000 in Van, but LNT incidences are low for both provinces. Of the extrapolmonary TB cases in Turkey, extrathoracic LNT is reported in 26.7% and intrathoracic LNT in 5.5% of the cases. However, separate data for each province have not been published (7,8).

In the present study, records of the clinical features and the socioeconomic and demographic characteristics of patients with LNT were retrospectively investigated in regional dispensaries. Data were evaluated for comparing two different provinces for LNT.

MATERIALS AND METHODS

Setting: In the Turkish healthcare systems, dispensaries are the official locations where TB drugs are distributed to patients free of charge and where patients are followed up for therapy and treatment outcomes. Two regional dispensaries that were separated by the farthest distance possible in the country were included in the study. The first was one of the eight central dispensaries in the western city of Izmir, the third largest city in Turkey. The second dispensary was in Van in Eastern Turkey. The populations of these two provinces have different demographic and socioeconomic characteristics (Table 1 and Fig. 1).

Study subjects: Records of LNT patients who had visited the dispensaries between 2000 and 2005 were...
Methods: Medical history records and physical examination details were reviewed for all patients. Definitive diagnosis was established by histopathological, bacteriological, and radiological methods. TST was performed in 44 patients. PPD test tuberculin (BB-MCIPD, Sofia, Bulgaria; 5 TU/0.1 ml) was applied intradermally (0.1 ml, or 5 TU). Skin responses were evaluated 72 h after application, with a transverse diameter of induration ≥ 10 mm being judged as a positive reaction.

In order to detect pulmonary manifestations, all subjects underwent chest radiography, and were asked to provide sputum samples for analysis. Only 9 patients could give the sputum sample. Patients showing cavernous or disseminated patterns on the radiographs and patients with smear test (i.e., Ziehl-Neelsen staining) results that were positive for the presence of acid-fast bacilli in sputum samples were excluded.

Histological and/or microbiological analyses for the presence of mycobacteria in lymph node tissue were conducted in all patients (except 2 patients who were diagnosed on the basis of just clinical and radiological findings). Fine-needle aspiration (FNA) and lymph node excision and incision were used to investigate superficial lymph nodes (i.e., cervical, axillary, or inguinal lymph nodes). TB was diagnosed in the mediastinal nodes by testing specimens from a bronchoscopic fine-needle biopsy. Mediastinoscopy and video-assisted thoracoscopic surgery (VATS) were performed for mediastinal nodes.

One aliquot of the FNA sample was fixed in 95% ethyl alcohol and stained by Giemsa for cytological analysis. A second aliquot was used for microscopic detection using Ziehl-Neelsen staining and culturing on Lowenstein-Jensen medium and/or radioactive culture (BACTEC; Becton Dickinson, Sparks, Md., USA) in cases in which bacteriological examinations were available. The same procedure was followed for samples from lymph node excisions. Histological analyses were performed on samples fixed in formalin.

Definition of socioeconomic status: Socioeconomic status was defined at household and regional levels, and was determined on the basis of the following parameters: (i) human resources, (ii) education, and (iii) access to community infrastructures and facilities (Fig. 1).

Statistics: SPSS 15 software was used for statistical analysis. Distribution of data was evaluated using the Kolmogorov-Smirnov test. Analysis of parametric variables was performed using the t test. Kruskal-Wallis and Mann-Whitney tests were applied for nonparametric variables. Chi-square tests were used for analyzing categorical data.

Analysis of patient records was performed according to the Helsinki declaration of 2008.

RESULTS

Van and Izmir account for 1.3% and 5.3% of the population of Turkey, respectively. In Van Province, 32.5% of the population lives in urban areas, whereas 85% of the population resides in cities and towns in Izmir Province. In Turkey, 70.3% of the total population lives in urban settings (10).

Between 2000 and 2005, a total of 109 cases were diagnosed as LNT in both provinces. In Izmir Province, 56 (24.8%) patients were enrolled from 225 patients with extrapulmonary disease. According to the study inclusion criteria, these patients were classified into two groups: 48 (21.3%) patients were classified into the LNT group, and 8 (3.5%) patients were classified into the LNT-PM group. In Van, 53 (30.8%) LNT patients were reexamined retrospectively. A total of 109 LNT cases from Van and Izmir Provinces were included in the study. Patients were divided into two groups: LNT and LNT associated with pulmonary manifestations (LNT-PM).

Table 1. Demographic features of two provinces

<table>
<thead>
<tr>
<th>Age group (y)</th>
<th>Izmir</th>
<th>Van</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>Total</td>
<td>797,900</td>
<td>415,900</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>410,100</td>
<td>217,800</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>387,800</td>
<td>198,100</td>
</tr>
<tr>
<td>15–64</td>
<td>Total</td>
<td>2,243,600</td>
<td>441,300</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1,089,400</td>
<td>220,300</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1,154,200</td>
<td>221,000</td>
</tr>
<tr>
<td>&gt;65</td>
<td>Total</td>
<td>229,500</td>
<td>20,240</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>99,500</td>
<td>9,940</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>130,000</td>
<td>10,300</td>
</tr>
</tbody>
</table>

*expenditure of total consumption
The LNT-PM patients also had additional disorders, including arthritis, systemic lupus erythematosus. Three patients had cardiac disorders, and gastritis; and 1 had rheumatoid arthritis, systemic lupus erythematosus. Three (20%) of the LNT-PM patients also had additional disorders (malignancy, thyroid disorder, and chronic renal failure).

There were significantly higher cases of LNT in women in Van than in Izmir (P = 0.0006). There was no difference in terms of gender in the distribution of LNT-PM cases (P > 0.05). LNT patients in Izmir were significantly older than those in Van (P = 0.005), while the ages of the LNT-PM patients in Izmir and Van were not significantly different. Similarly, there was no difference in the ages of LNT and LNT-PM patients from the same region (P > 0.05). No difference in TB contact history between case groups was detected (P > 0.05). PPD-testing rates in LNT patients were higher in Izmir than in Van (P = 0.0003), as was the positivity of TST testing (P = 0.01). The rate of BCG vaccination in both the LNT and LNT-PM groups in Izmir was much higher than those in Van (P < 0.0001 and P = 0.0007, respectively). No differences were detected in terms of predisposing factors between the two groups.

The distribution of LNT cases according to age is shown in Fig. 2. Cases were more prevalent in the age range of 21–30 years for both LNT groups (P < 0.05). Cases were also more prevalent in the early decades in Van.

None of the patients had alcohol dependence, although 10 (34.5%) declared a smoking habit with a mean duration of 10 years. Additional disorders were found in 20 (22.2%) LNT patients. Three patients had chronic renal failure; 2 each had diabetes mellitus, malignancy, acute rheumatic fever, psychotic disorders, cardiac disorders, and gastritis; and 1 had rheumatoid arthritis, systemic lupus erythematosus. Three (20%) of the LNT-PM patients also had additional disorders.
Table 3. Clinical symptoms and diagnostic procedures of the LNT patients

<table>
<thead>
<tr>
<th>LNT patient</th>
<th>LNT-PM patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Izmir (n = 48)</td>
<td>Van (n = 46)</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Palpable mass</td>
<td>26 (51.4)</td>
</tr>
<tr>
<td>Weakness</td>
<td>5 (10.4)</td>
</tr>
<tr>
<td>Night sweat</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (10.4)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (4.1)</td>
</tr>
<tr>
<td>Lack of appetite</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Sputum expectoration</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td><strong>Histopathological diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Excision</td>
<td>47 22*</td>
</tr>
<tr>
<td>Incision</td>
<td>2* 3</td>
</tr>
<tr>
<td>Fine needle</td>
<td>12* 5</td>
</tr>
<tr>
<td>Bacteriological tests performed</td>
<td>13 13</td>
</tr>
<tr>
<td>Positive</td>
<td>1 0</td>
</tr>
<tr>
<td>Clinico-radiological diagnosis</td>
<td>1 1</td>
</tr>
</tbody>
</table>

*Total number of cases are unknown.
Abbreviations are in Table 2.

Fig. 3. Localizations of lymphadenopathies in total LNT patients.

Fig. 4. Localizations of lymphadenopathies in total LNT-PM patients.

histopathologically; however, the method of biopsy retrieval was not found in the patient records. Symptoms and diagnostic features of the cases are shown in Table 3.

A total of 99 lymphadenopathies (51 in Izmir and 48 in Van) were performed in the 94 LNT cases. In 5 cases, multiple nodes were encountered. Lymphadenopathies were most frequently (56.5%) localized to the cervical region (P < 0.001). There was no significant difference in lymph node localization between the Van and Izmir LNT groups (P > 0.05). Cervical and mediastinal nodes were detected at the same frequency in LNT-PM patients, and there was no significant difference in their occurrence between the two provinces. The localization, number, and proportions of the lymphadenopathies are shown in Figs. 3 and 4.

In addition, 1 case of larynx TB and 1 case of bone and parotid TB were detected in the Izmir and Van LNT groups, respectively. Three cases were associated with pulmonary TB in the LNT-PM group.

Chest radiograms were found to be normal in 90 (95.7%) of the LNT cases. Chronic fibrotic pulmonary changes were detected in 4 cases, with hilar enlargement being observed in 2 (mediastinal lymphadenopathy) of these 4 cases. Hilar enlargement was encountered in 10 (66.6%) cases; chronic fibrotic changes, in 2 (13.3%) cases, and pulmonary infiltration, in 3 (20%) LNT-PM cases.

Significant variables predicting LNT in the study included an age of 20–30 years, palpable cervical node, BCG vaccination, positive TST, and mediastinal lymph node involvement in LNT-PM cases.

Variables considered to be indicators of socioeconomic status were not generally associated with TB infection, but prevalence of TB infection tended to be higher in wealthier categories.

**DISCUSSION**

Effective treatment regimens and improved living standards have helped to decrease the incidence of TB in most geographic areas in the world. However, the spread of HIV infection and resistance to drugs for treating TB have limited the control of the disease, as a result of which TB has reemerged in some regions. Although the occurrence of pulmonary TB infection fluctuates, the incidence of extrapulmonary TB has continued to increase (9).

The incidence of LNT in Turkey ranges from 6.8–
43%, and LNT is the second most common form of extrapulmonary TB after TB pleuritis according to the literature (7,8,11,12). In addition, the incidence of LNT has been reported to be between 0.06-5.4% of all TB cases in Turkey (13–15). In our study, LNT was found in 21.3% and 26.7% of the extrapulmonary cases in Izmir and Van, respectively.

In agreement with previous studies, our findings showed that although in some areas of lower socioeconomic status, the incidence of TB was higher in males, LNT was more frequent in females (14,16,17). Dundapat 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 (18).

In regions of high prevalence, people are more commonly exposed to TB bacilli and show signs of disease at an earlier age. LNT is an early post-primary manifestation of TB. While Van Province represents the characteristics of developing countries, Izmir has the socioeconomic conditions of more developed countries, and therefore, it was expected that the patient features in these two provinces would be different. Thus, poorer socioeconomic conditions could explain the high incidence of cases at younger ages in Van Province, while older age (with associated diseases of old age) promoted reactivation of TB in Izmir. It is also thought that one of the reasons underlying the lower incidence of TB cases in Van is the reporting errors associated with issues of compliance to the national TB program (8).

Although BCG vaccination is mandatory in Turkey, it cannot be performed regularly in every district. TST values are not useful for the diagnosis of TB due to the moderate prevalence of TB and of BCG vaccination. Studies have shown that TST positivity is between 24–77% in the worldwide population, while it is 56–69% in TB patients in Turkey (19). Therefore, TST is a valuable, but non-specific, test for the assessment of TB patients in Turkey. The BCG vaccination rate was higher in Izmir Province than in Van Province while TST positivity was similar in the two provinces. While this could be seen as a normal result of the vaccination ratio, it could also indicate enhanced immune responses to TB infection and/or BCG due to better living standards. It is difficult to distinguish between these possibilities. In the literature, correlations between TST positivity and prior history of contact with TB patients were reported, which could help in the diagnosis of LNT, especially in pediatric patients. However, in an adult group, TST has less diagnostic value (13). In areas of high prevalence, high rates of BCG vaccination can lead to a high rate of false-positive TSTs in the healthy population. False-positive reactions to the TST have also been clearly identified in patients previously infected with nontuberculous mycobacteria. This renders interpretation of positive TSTs difficult, especially in situations where symptoms of an active TB infection are not present (19,20). However, false-negative reactions to the TST can also occur since a proportion of individuals that harbor latent TB does not react to the test. This is particularly the case with infants or HIV-infected patients who have been recently exposed to communicable TB. Another notable group of false-negative TSTs are those in which there is significant induration but which are erroneously interpreted as negative by health professionals (21). Thus, although TST positivity was high in the present study, it was not considered to be a strong indicator for LNT.

There is significant variability in the literature on the occurrence of clinical signs and symptoms of LNT. Jha et al. have noted that weakness, night sweats, and cough occur in 17.8%, 10.3%, and 10.3% of the patients, respectively (16). The most frequent complaint was cervical mass (46%). Dundapat et al. reported weight loss in 85% and fever in 40% of patients (18). The literature supports our findings that LNT patients declare their symptoms according to their perception of their own body and health and their ability to express themselves, which is based on their socioeconomic and educational levels.

According to WHO TB guidelines published in 1997, pulmonary parenchymal invasion should be limited to extrapulmonary TB cases. Pulmonary TB refers to a disease involving the lung parenchyma. Therefore, tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB is considered to have pulmonary TB (22). Priel et al. have found that 28.8% of LNT cases have pulmonary TB (23). In Turkey, particularly in studies originating from hospitals that treat patients with chest diseases, mediastinal LNT together with pulmonary TB is seen at rates as high as 7.5–20% (4,5). We found that 3 cases in the LNT-PM group with mediastinal lymphadenopathy were diagnosed before pulmonary TB.

Interpretation of results can be difficult due to the two-stage nature of TB, which is characterized by an infection and a disease stage. Generally, studies do not clearly differentiate between TB infection and TB disease, and it is not clear how socioeconomic conditions are associated with the risk of infection and the risk of developing disease, or both (20).

In most previous studies (24–26), data suggest a strong influence of both household crowding and socioeconomic status on the risk of TB infection. Crowding and socioeconomic status perhaps underlie different causes of TB infection: (i) infections at the household level, which occur through overcrowding in poor households; and (ii) infection at the community level. Wealthier households likely reflect a more urban-type setting, characterized by a greater population density and a higher chance of human interaction, which is likely to foster TB transmission. This effect has been demonstrated in previous studies, which show that in settings with a high prevalence of TB, especially densely populated settings, extensive TB transmission can occur via complex social networks that are likely to be as important as household contact in facilitating transmission (27,28).

The limitations of the present study that should be acknowledged include probable reporting errors in Van Province and a relatively low patient number.

In summary, LNT occurs as a frequent extrapulmonary form of TB among females, and young adolescents have a significantly higher susceptibility, especially in
provinces of lower socioeconomic status. Symptoms are variable and people either gender and any age are under risk in regions of moderate to high TB prevalence. The TST is not helpful for diagnosis. In the presence of mediastinal lymphadenopathy, pulmonary TB should be suspected. LNT should be the primary consideration in the differential diagnosis of lymphadenopathies, particularly in cervical cases.

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Conflict of interest None to declare.

REFERENCES