

Extrapulmonary Tuberculosis Cases in an Infectious Diseases Department

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What is already known on this topic?

- Extrapulmonary tuberculosis (TB) accounts for a significant proportion of TB cases worldwide, with varying prevalence across different regions.
- Diagnosis of extrapulmonary TB is often challenging due to its diverse clinical manifestations, leading to delayed treatment.
- Previous studies indicate that pulmonary TB cases predominantly present to chest diseases departments, while extrapulmonary cases may be identified in various clinical settings.

What this study adds on this topic?

- This study highlights a high prevalence (85%) of extrapulmonary TB among hospitalized TB patients in an infectious diseases department, differing from national reports.
- Miliary TB was the most common extrapulmonary form in our study, contrasting with previous findings where pleural TB was more frequent.

Abstract

Objective: Tuberculosis (TB) remains a significant public health problem in Türkiye. We aimed to document cases diagnosed as TB while being investigated for fever of unknown origin, meningitis, pleurisy, lymphadenopathy, and other clinical pictures in an infectious diseases department.

Methods: We reviewed the records of the Infectious Diseases Department of a Medical Faculty retrospectively and evaluated all patients with *Mycobacterium tuberculosis* infection hospitalized between January 1989 and October 1998.

Results: One hundred eighty-four cases diagnosed as TB were enrolled. Forty-seven percent of the patients were male. Mean age was 30 years (range: 14-76). Extrapulmonary TB was diagnosed in 157 (85%) of the patients. The distribution of the cases was as follows: miliary (27%), lymphadenitis (21%), meningitis (12%), pleural (12%), peritoneal (14%), bone (7%), and other (10%). Pulmonary TB frequency was 15%. Tuberculin skin tests were positive in 85 of 164 patients. The methods of diagnosis were acid-fast smear (60/184), culture (17/184), histology (101/184), and clinical/radiological/therapeutic test (72/184).

Conclusion: Extrapulmonary TB is still a persistent problem in Türkiye. This study highlights the unique spectrum of extrapulmonary TB observed in a tertiary care center, with miliary TB being more prevalent than in national and international reports, emphasizing the need to consider departmental focus and patient demographics.

Keywords: Extrapulmonary, lymphadenitis, meningitis, miliary, pleurisy, tuberculosis

Introduction

Although it is one of the oldest pathogens known to humankind, tuberculosis (TB) remains a crucial clinical and public health problem worldwide. As surprising as it may be, findings suggestive of Pott's disease (tuberculous spondylitis) were found in the remains of a 15-year-old boy who lived in the fourth millennium BC.¹ Egyptian mummies also reveal TB was an issue in the region at the time.^{2,3} Thousands of years have passed since we made acquaintance with this *Bacillus*; however, TB remains a major health problem. According to the World Health Organization (WHO) Global Tuberculosis Report 2022, 10.6 million people throughout the world, who were HIV-negative, fell ill with TB (134 cases/100 000 population), and 1.4 million died of it in 2021. Unfortunately, the incidence rate of TB seems to have increased compared to the previous year.⁴ Tuberculosis is the 13th cause of death globally.⁵

Extrapulmonary TB case rates compared to pulmonary TB worldwide are inconsistent. Some studies report rates around 15% of all TB cases,^{6,7} while others indicate higher numbers, such as 19%-20% in certain South Asian countries like Afghanistan, Bangladesh, India, and Pakistan,⁸ 21.3% in China,⁹ 29.2% in Pakistan,¹⁰ 32.6% in Portugal,¹¹ and even 60.5% in Mexico.¹² The Turkish Ministry of Health states that extrapulmonary TB occurs in 34.3% of all tuberculosis cases.¹³ Conflicting results exist regarding the rates of extrapulmonary and pulmonary TB. Özbay et al¹⁴ found the rate of extrapulmonary TB cases to be 48.2%,¹⁴ while Akgün et al¹⁵ reported it as 53.8%.

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As pulmonary TB cases present with coughing, sputum, chest pain, and sometimes hemoptysis, they are more likely to apply to chest diseases departments. Diagnosis of TB can also be made while investigating patients with fever of unknown origin, pneumonia, pericarditis, and other clinical conditions. In this study, we aimed to document the spectrum of extrapulmonary TB cases in an infectious diseases department.

Methods

The ethical approval for the study was obtained from the Demiroğlu Bilim University Clinical Trials Ethical Committee (Approval form number: 44140529/29488, Date: July 18, 2023).

The study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with all international and national laws and regulations. Due to the retrospective nature of the study, informed consent from the patients was not obtained. Informed consent was only taken from the institution from which the medical records of the patients were accessed.

We reviewed the records of the Infectious Diseases Department of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine retrospectively and evaluated all patients with *Mycobacterium tuberculosis* infection hospitalized between January 1989 and October 1998.

Among the data of the patients, gender, age, extrapulmonary TB sites, diagnostic methods, presence of underlying disease, and whether they used immunosuppressive drugs were recorded.

In diagnosing extrapulmonary TB, at least 1 of these 3 criteria was sought:

1. Demonstration of acid-fast *bacilli* in direct smear or Löwenstein–Jensen culture from material obtained from an extrapulmonary site (e.g., pleural fluid, urine, gastric aspirate, lymph node aspirate, etc.).
2. Presence of caseating granulomas in biopsy material, with or without acid-fast *bacilli* positivity.
3. Clinical findings are consistent with tuberculosis, a positive tuberculin skin test, and a favorable response to tuberculosis treatment.

In pulmonary TB cases, the diagnosis was primarily based on positive sputum acid-fast staining and Löwenstein–Jensen culture results. All patients suspected of pulmonary TB underwent a pulmonary radiological evaluation, including posteroanterior chest x-ray imaging and thoracic computed tomography (CT) scans, which demonstrated pulmonary involvement.

Miliary TB cases were also evaluated radiologically, with typical miliary patterns and acinar opacities observed on chest imaging (posteroanterior chest x-rays and thoracic CT scans). For diagnosing TB pleurisy and peritonitis, suspected patients underwent diagnostic thoracentesis and paracentesis. Analysis of pleural and peritoneal fluid revealed an exudative pattern with lymphocyte predominance.

In patients with lymphadenitis, an excisional biopsy of affected lymph nodes confirmed the diagnosis of TB histologically.

Bone TB was diagnosed through fine-needle aspiration or biopsy, with specimens evaluated histologically and microbiologically.

All patients diagnosed with TB meningitis underwent lumbar puncture to obtain cerebrospinal fluid, which revealed increased lymphocyte counts, elevated protein levels, and decreased glucose levels. Patients were also referred to Neurology for consultation and underwent cranial CT scans.

Table 1. Pulmonary and Extrapulmonary TB Cases

Site	Number of Patients (% of all TB Patients)
Pulmonary	27 (14.67%)
Miliary	42 (22.83%)
Lymphadenitis	33 (17.93%)
Meningitis	19 (10.33%)
Pleurisy	19 (10.33%)
Peritoneal	17 (9.24%)
Bone	11 (5.98%)
Other	16 (8.69%)

Results

One hundred and eighty-four patients diagnosed with TB and hospitalized in the infectious diseases department during a 10-year period were included in the study. Ninety-eight (53.26%) of the patients were female, and 86 (46.74%) were male. The mean age of the patients was 30 (range: 14-76 years).

Twenty-seven (14.67%) out of 184 TB cases had pulmonary TB, whereas extrapulmonary TB was diagnosed in 157 of the patients (85.33%). The most common extrapulmonary TB form was miliary TB in our study (42 patients, i.e., 26.75% of the extrapulmonary TB cases). The rest of the extrapulmonary TB sites were as follows in decreasing order: 33 (21.02%) patients had lymphadenitis, 19 patients (12.10%) had meningitis, 19 patients (12.10%) had pleurisy, 17 (10.83%) patients had peritoneal TB, 11 (7%) patients had bone TB, and the remaining 16 (10%) patients had TB at other extrapulmonary sites. Pulmonary and extrapulmonary TB cases are shown in Table 1.

The distribution of extrapulmonary involvement sites in our cases is shown in Figure 1.

Methods used for diagnosis were as follows: histology in 101 patients (54.89%), clinical/radiological diagnosis in 72 patients (39.13%), acid-fast smear in 60 patients (32.60%), and tuberculosis culture in 17 patients (9.24%). The tuberculin skin test was performed in 164 TB patients and was positive in 85 (51.83%) of the patients (Table 2).

As for the concomitant diseases and drug use: 5 (2.72%) patients with TB had malignant diseases (Hodgkin's lymphoma, non-Hodgkin's lymphoma, gastric cancer, acute myeloid leukemia,

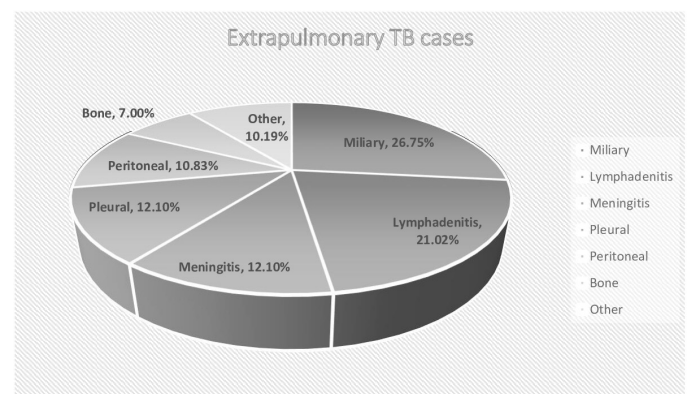


Figure 1. The distribution of extrapulmonary cases.

Table 2. Methods Used in the Diagnosis of TB Patients

Diagnostic Methods	Number of Patients (%)
Histology	101 (54.89%)
Clinical/radiological	72 (39.13%)
Acid-fast smear	60 (32.60%)
Tuberculosis culture	17 (9.24%)

and non-small cell lung cancer), 4 (2.17%) patients had diabetes, 3 (1.63%) patients had chronic obstructive lung disease (COPD), 3 (1.63%) patients had systemic lupus erythematosus (2 of them on steroid therapy and 1 under steroid plus azathioprine therapy), 2 (1.09%) patients had epilepsy, 2 (1.09%) patients had vasculitis, 2 (1.09%) patients had chronic hepatitis (due to hepatitis B and hepatitis C), 1 (0.54%) patient had liver cirrhosis, 1 (0.54%) patient had chronic renal failure, 1 (0.54%) patient had nephrotic syndrome (due to amyloidosis), 1 (0.54%) patient had rheumatoid arthritis, and 1 (0.54%) patient had measles (Table 3). None of our patients tested positive for HIV.

Discussion

In our study conducted in an Infectious Diseases Department, rather than a Pulmonary Diseases Department, the overall rate of extrapulmonary TB cases among all tuberculosis cases admitted to the clinic was 73%, significantly higher than the national Ministry of Health reports.¹³ Unfortunately, the national Ministry of Health data do not include statistics on the rate of extrapulmonary TB cases for the specific time frame of our research, making it impossible to compare our findings with official national data for that period. We believe the primary reason for the higher extrapulmonary TB rate in our study compared to national data is that the majority of pulmonary tuberculosis cases tend to present directly to Pulmonary Diseases Departments, both before and after diagnosis, primarily due to their predominant pulmonary symptoms.

While the ratio of men and women is approximately equal for pleural TB in our country, extrapulmonary TB involvement is more

common in women.¹⁶ In our study, we observed a slight female predominance in extrapulmonary TB cases similar to some other studies.^{8,10,17,18} While Li et al⁹ found extrapulmonary TB was more common in males. In another large-scale multi-centre observational study conducted in China, among hospitalized extrapulmonary cases, the male/female ratio was 1.51, indicating a male predominance.¹⁹ The male/female ratio in our study is 0.88.

According to the data presented by the Turkish Ministry of Health, extrapulmonary TB cases from the most common to the least common in our country are listed below¹⁶:

Pleural tuberculosis,
Extrathoracic TB lymphadenitis,
Intrathoracic TB lymphadenitis,
Peritoneal/gastrointestinal TB.,
Genitourinary TB.,
Non-vertebral bone-joint TB.,
Vertebral bone-joint TB.,
Miliary TB.,
Meningeal TB.,
Central nervous system TB (non-meningeal).,
Other organ TB.

We found miliary tuberculosis to be the most common extrapulmonary TB form among our patients, consisting of 22.83% of the cases (42 patients). In their research on the distribution of extrapulmonary TB cases among hospitalized patients between 1997 and 2003, Tavusbay et al¹⁷ found that pleural TB was the most common form in the chest diseases department of a Chest Diseases and Surgery Research Hospital in Türkiye, accounting for 67.6% of all extrapulmonary TB cases. The second most common extrapulmonary TB form was lymphadenitis (19.5%). In a similar time frame, from 1997 to 2004, Akgün et al¹⁵ found that the most common extrapulmonary TB site was the pleura; however, pleurisy cases due to TB accounted for only 19% of all extrapulmonary TB patients. In Pakistan, where TB continues to be a major public health problem, the most common cause of extrapulmonary TB has been shown to be tuberculous pleurisy.¹⁰ A national cross-sectional Chinese study states that the most common extrapulmonary TB form is tuberculous pleurisy (35%),⁹ a similar study shows a similar result, with tuberculous pleurisy found to be 50.1% of all cases, whereas another study from the same country reports skeletal TB to be the most common (41%) extrapulmonary TB form among hospitalized patients.²⁰ Chaw et al found lymphatic and pleural TB to be the most common extrapulmonary TB forms, constituting 44.8% and 19.4% of all extrapulmonary TB cases respectively.²¹ Although the most common cause of extrapulmonary TB varies in different studies conducted in different countries, and one of the most common causes of extrapulmonary TB in studies conducted in our country is pleural TB, in our study we observed that pleural TB is the fourth most common cause of extrapulmonary TB. Again, we believe this is due to the fact that the clinic where we conducted our study was an infectious diseases department, not a pulmonology department.

This study sheds light on the unique spectrum of extrapulmonary TB cases observed in a tertiary care center, emphasizing the distinct characteristics linked to the infectious diseases department setting. The predominance of miliary TB in our cohort highlights a deviation from both national and international reports, which often identify pleural TB or lymphadenitis as the most prevalent forms. This variation underscores the importance of considering the departmental focus and patient demographics when interpreting and comparing TB data across different healthcare institutions.

Table 3. Diseases Accompanying TB

Concomittant Diseases	Number of Patients (%)
Malignancy	5 (2.72%)
Diabetes	4 (2.17%)
COPD	3 (1.63%)
SLE	3 (1.63%)
Epilepsy	2 (1.09%)
Vasculitis	2 (1.09%)
Chronic hepatitis	2 (1.09%)
Liver cirrhosis	1 (0.54%)
Chronic renal failure	1 (0.54%)
Nephrotic syndrome	1 (0.54%)
Rheumatoid arthritis	1 (0.54%)
Measles	1 (0.54%)

Our findings also reflect the evolving challenges in diagnosing and managing extrapulmonary TB, particularly in resource-limited settings. Early recognition and accurate differentiation of these atypical presentations remain critical to improving patient outcomes and guiding appropriate therapeutic strategies.

Looking ahead, we aim to extend this research by analyzing extrapulmonary TB cases over the next 3 decades. This longitudinal approach will provide an opportunity to examine temporal trends and shifts in disease patterns, potentially influenced by changing socioeconomic factors, advancements in diagnostic tools, and the impact of public health initiatives. Such a comprehensive analysis may offer valuable insights into the broader epidemiology of extrapulmonary TB, ultimately contributing to improved prevention, diagnosis, and management strategies.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: The ethical approval for the study was obtained from the Demiroğlu Bilim University Clinical Trials Ethical Committee (Approval no.: 44140529/29488, Date: July 18, 2023).

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