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TANAFFOS

Assessment of Clinical, Histopathologic, and Radiologic Features in Extrapulmonary Tuberculosis Patients

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Background: Tuberculosis (TB) is clinically divided into two categories: pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB). PTB has many different manifestations, and sometimes the initial diagnosis is challenging and depends on the prevalence of infection as well as the experience and development of local medical centers. Thus, we aimed to review all EPTB patients in our referral center.

Materials and Methods: This retrospective study reviewed all confirmed cases of EPTB referred to a referral/general center within the last decade.

Results: This study included 68 cases of EPTB. Percentages of males and females were 58.8% and 41.2%, respectively. The majority of EPTB patients were TB meningitis (44.1%), followed by musculoskeletal TB (17.6%). About 8.8% of patients had a positive culture. The acid-fast bacilli test was found to be positive in 19.1% of cases. The mortality rate in this study was 19.1% and the highest rate of mortality was observed in intestinal and mesenteric TB (33.3%).

Conclusion: According to this study, the majority of hospitalized EPTB patients had TB meningitis. The mortality rate in intestinal and mesenteric TB was higher compared to other types of EPTB, probably due to delayed diagnosis. In the current study, Positive results for smears and cultures were also low.

Keywords: Extrapulmonary tuberculosis; Mortality; TB

INTRODUCTION

Tuberculosis (TB) is a granulomatous infectious disease that can attack any organ or tissue. It has various manifestations and is divided into two categories of pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB) (1, 2). TB is one of the oldest and most deadly infectious diseases in the world. Despite all efforts to reduce the burden of the disease, it remains a major public health problem, especially in developing countries (3). In 2022, 7.5 million people were infected with tuberculosis, which 55% of whom were men, 33% were women, and 12% were children (aged 0–14 years). In the same year, 1.30 million (range, 1.18–1.43 million) people died from tuberculosis (4).

EPTB affects all organs except the lungs (genitourinary system, skin, bones, joints, meninges, etc.). If a patient with extrapulmonary tuberculosis has a lesion in the lung, the patient is classified as a pulmonary tuberculosis patient. EPTB accounts for 15-20% of all patients with tuberculosis. Due to the variety of EPTB manifestations, its initial diagnosis is sometimes very difficult. EPTB Manifestations could be only constitutional symptoms such as fever, anorexia, weight loss, and fatigue without focal site symptoms and signs. Diagnosis of EPTB is also more difficult than PTB, which requires invasive procedures such as biopsy and surgery in addition to the usual procedures (2).

Depending on the prevalence and incidence of mycobacterial infections in a geographic region and the experience and familiarity of health professionals with this entity and the evolution of health infrastructure, the frequency and manifestations of EPTB can be different and problematic issues. The purpose of this study was to identify the frequency, clinical, histopathological, and radiological characteristics of EPTB patients referred to or admitted to our center over the last decade.

MATERIALS AND METHODS

We designed a retrospective study of EPTB cases who had been diagnosed in a tertiary training/general hospital. The study was approved by the local Ethics Committee of the Institution with the ethics code IR.SBMU.MSP.REC.1400.194 and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

This study included 68 patients with extrapulmonary tuberculosis who were diagnosed between 2011 and 2021 in Loghman Hakim Hospital in Tehran. The criteria for entering the study were having a definite diagnosis of extrapulmonary tuberculosis based on molecular (PCR), histopathological, and positive smear or specimen culture evaluation, and the possibility of full access to information related to the individual's disease. The criteria for exiting the study included not having a definite diagnosis or incomplete patient information. Demographic, clinical, laboratory, and radiological data for cases of extrapulmonary tuberculosis diagnosed in Loghman Hakim Hospital in Tehran were obtained retrospectively from registered documents.

The EPTB cases were evaluated in terms of the marital situation, age, gender, co-morbidity, underlying disease, history of previous TB, TST (tuberculin skin test), cytology, Ziehl-Neelsen staining and culture, radiological and histopathological findings, diagnostic and therapeutic features, extrapulmonary organ involvement, and therapeutic outcome.

In this study, descriptive statistics were used to describe the distribution of qualitative data by expressing the frequency for qualitative variables.

Due to the retrospective nature of the study, the consent form was not obtained from the patients, but all the information of the examined patients was recorded and remained confidential. Also, there were no conflicts of interest for the project's executives in this study.

RESULTS

Sixty-eight EPTB cases were included in this study (Table 1). The mean ± SD age of participants was 41.1±18.2 years. Percentages of male and female participants were 58.8% and 41.2%, respectively. HIV (8.8%), HCV (1.5%), HIV and HCV infections (1.5%), and malignancies (4.4%) were the underlying diseases observed among participants. TB meningitis was the most common type of EPTB (Table 2).

Table 1. Type of extra-pulmonary TB

Type of extra-pulmonary TB	N	%
TB meningitis	30	44.1%
Musculoskeletal TB	12	17.6%
Intestinal and mesenteric TB	9	13.2%
Military TB	8	11.8%
Peripheral lymph node TB	2	2.9%
Spinal TB	2	2.9%
Nervous system TB	1	1.5%
Tuberculous Pleurisy	1	1.5%
Skin and subcutaneous TB	1	1.5%
Intrathoracic lymph node	1	1.5%
Genitourinary TB	1	1.5%
All	68	100

Diagnosis

The diagnostic methods varied among patients (Table 2). The most important and predominant radiologic findings in various types of infection were the following:
Tuberculosis meningitis: hydrocephalus (3/29), infract due to arteritis (1/29), tentorial enhancement (1/29), dilatation of fourth ventricles (1/29), dilatation of lateral ventricles (1/29), leptomeningeal enhancement (1/29), cerebral edema (1/29), nodular enhancement of meninges (1/29), and basal enhancing exhausted (1/29).

Table 2. Diagnosis of extrapulmonary tuberculosis

Type of TB	Clinical manifestation and imaging	Molecular	Microbiology	Histopathology	Combination
Tuberculosis meningitis	10.3%	3.4%	6.8%		79.5%
Musculoskeletal TB	41.3%				58.7%
Intestinal and mesenteric TB	22.2%				77.8%
Military TB	75%				25%
Peripheral lymph node TB	50%	50%			
Spinal TB	100%				
Tuberculous Pleurisy					100%
Skin and subcutaneous TB					100%
Intrathoracic lymph node					100%
Genitourinary TB				100%	

Bone and joint tuberculosis: periarticular osteoporosis and osteolytic bone destruction (3/12), destruction of vertebral bodies (2/12), spondylosis (1/12), intervertebral disc herniation (1/12), presacral abscesses (1/12)

Miliary TB (except for lungs): pericardial and pleural effusion (3/8) and ascites (2/8), diffused lymphadenopathy (1/8), microcalcification and pleural thickness (1/8),

Intestinal and mesenteric TB: haziness in the mesentery and change in the bowel gas pattern (1/9), abdominal ascites (1/9).

Cytopathological findings included caseating granulomatosis (4.4%), necrotizing granulomatous inflammation (2.9%), and non-necrotizing granulomatous inflammation (1.5%). TST results were positive in 5 patients, negative in 2 patients, and unremarkable in 8 patients. This test had not been performed for the remaining patients. About 8.8% of patients were positive for mycobacterial culture. Bacillus acid-fast staining was positive in 19.1% and negative in 22.1%. This test had not been performed for the remaining patients. The adenosine deaminase (ADA) test was positive in 14.7% of cases; 4.7% of patients had negative and 10.3% had unremarkable results. Also, this test had not been performed in the rest of the patients.

Treatment

Fifty patients received anti-tuberculosis antimicrobials, and eighteen were treated with a combination of anti-TB and surgical intervention. The percentage of surgical intervention in each group included spinal TB (100%), intestinal and mesenteric TB (66.7%), extra-axial bone and joint TB (58.3%), miliary TB (12.5%), and meningitis (6.8%).

Outcome

The mortality rate in this study was 19.1% and approximately 50% of patients had an appropriate treatment response during hospitalization. The mortality rates for each group vary: meningitis (23.3%), musculoskeletal TB (8.3%), miliary TB (25%), and the highest rate among intestinal and mesenteric TB cases (33.3%).

DISCUSSION

Based on the study of 68 hospitalized patients, the majority of EPTB patients had tuberculous meningitis, followed by musculoskeletal tuberculosis. The highest rate of mortality was observed in intestinal and mesenteric TB, and the lowest rate was reported in musculoskeletal TB, which was also the most responsive to treatment.

According to our study's findings, the percentages for males and females were 58.8% and 41.2%, respectively. The results were similar to other studies, showing a high proportion of men (5-7). Gender may be a factor related to the development of EPTB (8). However, the relationship between gender and TB manifestations has remained unclear (9).

Previous studies have shown that the localization of EPTB may be variable. Based on some studies, pleural TB is the most common EPTB in Sub-Saharan Africa, Poland,

Romania, and China (5, 8, 10). However, other studies have found that lymph node tuberculosis is the most common site of EPTB in the United States, the United Kingdom, Turkey, and the Netherlands (11-14). In a study from China, the genitourinary system and the skin were the common sites (15).

Based on previous studies, different forms of EPTB are common in different countries, and this may be related to various factors, such as the genetic factors of the population. For example, natural resistance-associated macrophage protein 1 (NRAMP1) encoded by the SLC11A1 gene may play an important role in the localization of *Mycobacterium tuberculosis* infection at the onset of infection (16). Therefore, the SLC11A1 polymorphism may play an important role in the host's defense against the development of tuberculosis. (17). Also, some genes from different strains of tuberculosis can make patients more susceptible to tuberculosis in other parts of the body, like the lymph nodes tuberculosis (18). Another factor that may be important is immunity to Bacillus Calmette-Guerin (BCG), as it has different protective effects against different forms of tuberculosis, and the countries have different policies on universal BCG vaccination (19, 20).

The frequency of TB meningitis in our study was higher compared to the other studies since our study included only hospitalized patients. In addition, some studies have shown that meningitis accounts for only 5-10% of EPTBs and 1% of all TB patients, but is more disabling than other forms of EPTB and increases the rate of hospitalization (21, 22).

The percentage of positive smears is low because most clinical specimens should be obtained from inaccessible sites; therefore, with the increasing probability of paucibacillary, the sensitivity of diagnostic tests decreases. Based on previous studies, smear sensitivity is low, with a range of 0% to 40%; so, a negative smear result does not exclude EPTB (23).

In the current study, the positive culture rate was low (8.8%). This could be due to a lack of technical skills and the low growth rate of bacteria in these cultures. In clinical practice, positive culture results were observed in less than half of the EPTB patients (24). The sensitivity of the result is between 30% and 80% and it takes 2-8 weeks to obtain the results. Hence, culture is not helpful in the timely treatment of patients(23). In most cases, culture was not taken from patients.

Most of our patients had meningitis TB, and although these patients had low smear-positive results, all had clinical symptoms and radiological findings. Based on previous studies, the bacteriological diagnosis of tuberculous meningitis is very difficult due to the paucibacillary nature of the disease site in TB meningitis, and the microbiological confirmation rate in the diagnosis of TB meningitis ranges from 10% to 87% of cases (25, 26). Therefore, diagnosis of TB meningitis depends on clinical manifestations, radiological findings, and the presence of extra-neural TB (27).

Surgical intervention is not usually used in extrapulmonary TB but is sometimes necessary to diagnose abnormal pathological lesions or local complications of invasive TB. In our study, about 13% of patients underwent surgical intervention due to complications of invasive TB. More than half of our intestinal tuberculosis patients had surgery. Although peritonitis is not a common complication of tuberculosis, it is a complication that every abdominal surgeon needs to consider (28).

Studies investigating risk factors for death in EPTB patients have shown that the presence of TB meningitis was associated with a poor prognosis (29). Consistent with this, in our study, TB meningitis was one of the sites of EPTB with high mortality. However, the number of patients in each group was small, and it was not possible to compare the mortality rates in each group. Also, TB meningitis is more threatening than other forms of tuberculosis (22, 28).

Our study's limitations were: 1) There was no post-discharge follow-up. 2) Our study was retrospective, and data collection relied on physician collection. 3) The study was a single-center study. 4) Some patients might not refer

to our center; therefore, the prevalence of EPTB may be underestimated. 5) Some patients discontinued the therapy in our center; therefore. the mortality rate may be influenced. 6) Our results did not study the EPTB in pediatrics because pediatric patients with TB were not hospitalized in our center.

CONCLUSION

According to the data of our study, the majority of EPTB patients had TB meningitis. Intestinal and mesenteric TB showed the highest mortality in these patients. Positive results for smears and cultures were also low.

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Conflict of interest

We declare no competing interests.

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