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Original article

Extrapulmonary tuberculosis: 7 year-experience of a tertiary center in Istanbul

Dılek Yıldız Sevgi [a,*], Okan Derin [a], Alı Seydı Alpay [a], Alper Gündüz [a], Ahmet Sanlı Konuklar [a], Banu Bayraktar [b], Emin Bulut [b], Nuray Uzun [a], Emıne Sonmez [c]

[a] Department of Infectious Diseases and Clinical Microbiology, Sisli Etfal Training and Research Hospital, Istanbul, Turkey
[b] Department of Clinical Microbiology, Sisli Etfal Training and Research Hospital, Istanbul, Turkey
[c] Department of Infectious Diseases and Clinical Microbiology, Istanbul Bilim University, Medical Faculty, Istanbul, Turkey

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ABSTRACT

Background: Although a decreasing trend of tuberculosis (TB) was reported in Turkey, higher proportion of extrapulmonary tuberculosis (EPT) was revealed.
Material and methods: In this retrospective study, clinical and laboratory data of 141 EPT patients were evaluated for a seven-year period by using descriptive statistics, and parametric and non-parametric tests where appropriate.
Results: The most frequent types of EPT were meningeal TB (23%) and TB lymphadenitis (21%), respectively. Other types of EPT were skeletal, miliary, peritoneal, abscess, genitourinarial, cutaneous and gastrointestinal involvement which ranged between 18% and 1%. Mean age was 42 and female/male ratio was almost equal. All patients were born in Turkey. Although all of them were permanent residents of Istanbul, 73% of the patients came from East and Southeast Region of Turkey. For the patients, being older than 40 years old ($p < 0.01$), having miliary TB ($p < 0.05$) and high CRP levels ($p < 0.05$) were found to be associated with mortality.
Conclusions: EPT still remains as a significant morbidity and mortality reason in lower income populations and developing countries. In our study, although all patients were residents of Istanbul approximately two thirds of them have migrated from East and Southeast parts of the country. The relatively high prevelance of tuberculosis cases in Istanbul may be due to the permanent migration from other parts of the country. Early diagnosis and initiation of appropriate treatment are the keys for reducing morbidity and mortality in patients with EPT, particularly in the cases of older ages.

1. Introduction

Mycobacterium tuberculosis has infected one third of world's population and causes 8.8 million new cases with approximately 1.1 million deaths each year. Since tuberculosis was declared as a public health emergency by World Health Organization (WHO) in 1993, several strategies including directly observed therapy short-course (DOTS) were introduced. Hundreds of thousands lives were saved in countries which adopted DOTS. Profound poverty, the HIV pandemic, civil wars, and refugee migration are challenges to success. Tuberculosis is the second infectious cause of death and major cause of morbidity [1,2].

Although the WHO Tuberculosis Report revealed that prevalence of tuberculosis has been decreasing worldwide since 2006, human being will be far away from achieving TB elimination even in 2050. In Turkey which is a developing country, the prevalence of tuberculosis is (including HIV) 25/100.000 [1]. Turkish Ministry of Health has published decreasing trends in annual tuberculosis report, recently. According to this report, the prevalence of tuberculosis dropped from 52/100.000 in 1990 to 25/100.000 in 2009. However, the proportion of extrapulmonary tuberculosis (EPT) has increased among all TB cases. The proportion increased from 28.6% to 35.4% between 2005 and 2009 [3]. Ozvaran et al. evaluated 14,266 patients with tuberculosis who were diagnosed between January 1999 and December 2003 in a tertiary care hospital in Istanbul in 2007. They reported that 2435 of those patients (17.1%) had EPTB [4].

The reasons of such an increase are still unclear in Turkey. Risk factors for EPT in the USA are reported as being HIV positive, being female, being non-Hispanic black, young age and having cirrhosis [5,6].

Conventional microbiological techniques have limitations for diagnosis of EPT [7,8]. Furthermore, a definitive diagnosis of EPT often requires an invasive procedure [9].

Tuberculosis may not only affect the lungs but also all the organs/tissues. Most frequent appearance of EPT is lymphadenitis [1]. Other forms of EPT are central nervous system (CNS)/meningitis, pleurisy, pericarditis, skeletal, genitourinary, gastrointestinal, peritonitis, cutaneous, etc.

The population of Istanbul is 14 million and it is the most crowded city of Turkey. In 2011, 5200 new TB cases were identified in Istanbul. EPT comprises 23% of all new cases [3]. Istanbul is settled over a large area. The patient population in the vicinity of our hospital represents a

* Corresponding author at: Merkez M. Lise S. Garden Homes Sitesi B Blok D.5 Kagithane, Istanbul, Turkey. Tel.: +90 533 410 16 84; fax: +90 212 373 51 96.
E-mail address: dileky26@hotmail.com (D.Y. Sevgi).

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heterogeneous group from low to high socioeconomic levels. Among all tuberculosis cases in Turkey, 32.7% were reported from Istanbul. Sisli Etfal Training and Research Hospital which is located on urban area of Istanbul is one of biggest healthcare provider with 900 beds.

We aimed to investigate demographic factors, clinical presentation, microbiologic characteristics and mortality rates of EPT in our patients.

2. Material and methods

We evaluated 150 EPT cases from medical records and outpatient reports for seven years, from January 2005 to December 2011 retrospectively. We investigated demographic, microbiologic characteristics of patients in the Department of Infectious Diseases and Clinical Microbiology of Sisli Etfal Research and Training Hospital in Istanbul-Turkey.

Patients with EPT included in the study were diagnosed either microbiologically/histologically or had high clinical suspicion in accordance with WHO diagnostic criteria [10]. Hospital computed database was searched for medical records, retrospectively. The patients who were followed for at least 6 months were included in the study. Nine patients were excluded after chart review: exclusion was made due to lack of data (3 patients) and loss of follow-up (6 patients). 141 patients were included in the study. We recorded age, gender and annual income of patients as demographic parameters and fever (>38.3 °C), weight loss (at least 5 kilogram loss of weight in 3 months, involuntarily), and night sweats as clinical parameters.

The results of hematologic, serologic and biochemical assays which were performed by the laboratory of Sisli Etfal Research and Training Hospital were obtained from each patient's record at initiation of diagnostic procedure.

Appropriate samples according to the site of infections were collected from patients and sent to microbiology laboratory. All samples were homogenized and, where required, decontaminated before inoculation. Each processed sample was cultured on *mycobacterium* growth indicator tube (MGIT) (Becton Dickenson, USA) and LJ medium. AFB staining was performed with Ziehl–Neelsen acid fast staining. A positive MGIT or positive LJ culture from each sample was identified as *M. tuberculosis* complex by hsp65 PCR-RFLP. 1% proportional drug susceptibility test was performed by using manual MGIT method. The drug concentrations of isoniazid (INH), rifampicin (RMP), ethambutol (ETM), streptomycin (STM) were 0.1 μg/m, 1 μg/ml, 3.5 μg/ml, 0.8 μg/ml, respectively.

All samples obtained by biopsy were sent to the pathology laboratory for histologic examination. Stained materials were evaluated in terms of caseification necrosis and chronic granulomatous inflammation.

Tuberculosis drugs were provided by Turkey Tuberculosis Dispensaries (VSD) free of charge and the patients with EPT were included in DOT program. Treatment was initiated with four-drug regimen (isoniazid [INH], rifampicin [RMP], pyrazinamide [PZA], streptomycin [SM]/ethambutol [EMB]). After two months of treatment with four-drug regimen, it was continued with two-drug regimen (INH and RMP) for 6–12 months based on the site of infection. According to our outpatient routine, the patients with tuberculosis were evaluated monthly. Physical examination, complete blood count, erythrocyte sedimentation rate, liver function tests were detected monthly. Radiologic investigation or invasive procedures were performed when required.

2.1. Statistical analyses

Statistical analyses were performed using Stata 12.0 (College Station, TX). Descriptive methods were carried out. Statistical significance was evaluated using *t*-test and χ^2 analyses. Because of small sample size, genitourinary TB, skin TB and TB abscess weren't evaluated for significance of mortality.

3. Results

We evaluated 150 EPT cases from medical records and outpatient reports for seven years, from January 2005 to December 2011 retrospectively. 141 patients were included. As mentioned before, nine patients were excluded. Some samples (28/141) achieved by invasive procedures were not investigated microbiologically due to either surgeon inconvenience or inappropriateness for laboratory admission. Diagnosis established by growth in culture was (86/113), by histological examination (55/75), by both culture and histological examination (34/45).

Demographic, clinical and laboratory findings are presented on Tables 1 and 2 respectively. In this study, the 2 most common diagnoses were meningeal TB (23%) and TB lymphadenitis (20%). Other types of EPT were skeletal, miliary, peritoneal, abscess, genitourinarial, cutaneous and gastrointestineal involvement which ranged between 18% and 3%. Mean age was 42 ± 17 and female/male ratio was almost equal. 68 (48%) patients were older than 40 years.

All patients were born in Turkey. Although all of them were permanent residents of Istanbul, 73% of the patients came from East and Southeast Region of Turkey.

Only one patient was anti-HIV positive. 103 patients were anti-HIV negative. HIV serology records were not available for 37 patients. There was neither obvious risk factors for HIV infection nor HIV-associated manifestations during treatment.

In 69 (49%) of the patients high fever was detected and fever was found as a significant finding in miliary tuberculosis ($p < 0.05$) rather than other types of EPT. Weight loss and night sweats were recorded for 52 (37%) and 48 (34%) of them, respectively.

Hemoglobin level and White Blood Cell count (WBC) were normal but mean Erythrocyte Sedimentation Rate (ESR) was 56 ± 41.5 mm/hour. Mean C-reactive protein (CRP) was 6.6 ± 8.3 fold. Mean of CRP elevation was found to be 3 times higher in the patients who died ($p < 0.05$).

In Cerebrospinal Fluid (CSF) WBC count was <100/mm^3 in 46%, between 100 and 250/mm^3 in 48%, 250–500/mm^3 in 12% and higher than 500/mm^3 in 4% of the patients. CSF/serum glucose ratio was <0.6 in 90% and <0.3 in 43% of the patients. CSF protein level was elevated in all patients except 3 cases, and it was detected >100 mg/dL in 52% of the cases.

Ziehl–Neelsen Acid-Fast Stain (AFS) staining and cultivation with *mycobacterium* growth indicator tube system were performed on bone marrow (n = 1), lymph node fine needle biopsy material (n = 20), bone biopsy material (n = 14), sputum (n = 6), peritoneal fluid/biopsy (n = 13), skin (n = 3), abscess (18), cerebrospinal fluid (31), endotracheal aspiration material (n = 3), and urine (n = 5). A summary of microbiological results are presented in Table 2.

Ninety one cases (65%) were administered anti-mycobacterial therapy based on the high-clinical suspicion without laboratory confirmation. Consequently, 71 of those (50%) were confirmed by further microbiological or pathological investigations. Mean duration between admission and initiation of anti-tuberculosis therapy was 8 weeks.

We found that being older than 40 years of age ($p < 0.05$), having miliary tuberculosis ($p < 0.05$) and high CRP levels ($p < 0.05$) were associated with mortality.

4. Discussion

World Health Organization declared that extrapulmonary tuberculosis (EPT) comprises 13% of all TB cases, approximately [1].

We found that in our cases the most common types of EPT were meningitis (23%) and lymphadenitis (21%)(Table 1). Peto et al. published a wide series of EPT cases from the USA and revealed that lymphatic (40%) and pleural (19.8%) types of EPT were the most frequent, and meningeal involvement was found in 5.4% of all cases [11]. Gunal et al. from Turkey reported wide range of EPT cases, officially recorded by VSD. According to this report, most common involvement was