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Evaluation of Culture-confirmed Extrapulmonary Tuberculosis Cases in a University Hospital

Bir Üniversite Hastanesinde Tanısı Kültür ile Doğrulanmış Akciğer Dışı Tüberküloz Olgularının Değerlendirilmesi

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Abstract

Introduction: Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* and can involve any organ, especially the lungs. In recent years, especially in developed countries, the incidence of TB has increased due to the growing number of people with acquired immunodeficiency. This has led to an increase in the incidence of extrapulmonary TB (EPTB). This study examined patients with EPTB confirmed by positive *M. tuberculosis* culture in İnönü University Faculty of Medicine, Department of Microbiology and Clinical Microbiology, Molecular Microbiology Laboratory.

Materials and Methods: Patients with positive *M. tuberculosis* culture in the molecular microbiology laboratory of our hospital between January 1, 2004 and December 31, 2014 were retrospectively evaluated according to culture-confirmed site of involvement, acid-fast bacillus (AFB), polymerase chain reaction (PCR) positivity, drug resistance, and mortality.

Results: The study included 132 patients; 41 (31.1%) were male and 91 (68.9%) were female. The mean age was 46.4±18.5 (17-86) years. Extrapulmonary TB types were TB lymphadenitis in 48 patients (36.4%), musculoskeletal TB in 23 (17.4%), disseminated TB in 17 (12.9%), urinary TB in 11 (8.3%), abdominal TB in 11 (8.3%), TB meningitis in eight (6.1%), pleural TB in six (4.5%), genital TB in five (3.8%), and cutaneous TB in three patients (2.3%). Acid-fast bacillus positivity rates were 21.7% in musculoskeletal samples, 16.6% in pleural samples, 12.5% in cerebrospinal fluid, 9% in urinary tract samples, and 6.2% in lymph nodes. Polymerase chain reaction positivity was not detected in cerebrospinal fluid or skin samples. The rate of resistance to at least one anti-tuberculous drug was 20%. Mortality was 16.1% (n=9) in the 56 patients (42.4%) with available data.

Conclusion: Lymphatic TB was the most common form in our patients. According to national data, pleural TB is among the common forms of EPTB in Turkey. However, the rate of pleural TB was low in our study due to the lack of pleural biopsy in our hospital during the study period. In TB-endemic regions such as Turkey, it is important to consider EPTB in the differential diagnosis of patients with relevant clinical findings and to confirm the diagnosis with TB culture primarily, as well as methods such as AFB staining and PCR.

Keywords: Miliary tuberculosis, spondylodiscitis, osteomyelitis, epidemiology, multidrug resistant tuberculosis

Öz

Giriş: Tüberküloz (TB), *Mycobacterium tuberculosis*'in neden olduğu, her organı etkileyebilen ama özeelikle akciğeri tutan bir hastalıktır. Son yıllarda, özellikle gelişmiş ülkelerde, kazanılmış immün yetmezliği olan kişilerde artışa bağlı olarak TB insidansı da artmıştır. Bu durum beraberinde ekstrapulmoner TB (EPTB) olgularında artışı getirmiştir. Bu çalışmada, İnönü Üniversitesi Tıp Fakültesi, Mikrobiyoloji ve Klinik Mikrobiyoloji Anabilim Dalı, Moleküler Mikrobiyoloji Laboratuvarı'nda *M. tuberculosis* üremesi olan EPTB olguları incelendi.

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Gereç ve Yöntem: Çalışmaya 01.01.2004 ve 31.12.2014 tarihleri arasında hastanemiz moleküler mikrobiyoloji laboratuvarında *M. tuberculosis* üremesi olan hastalar dahil edildi. Hastalar kültür üreme bölgelerine, aside dirençli basil (ARB)/polimeraz zincir reaksiyonu (PZR) pozitiflikleri, ilaç dirençleri ve mortalite durumlarına göre değerlendirildi.
Bulgular: Çalışmaya 132 hasta dahil edildi. Hastaların, 41'i (%31,1) erkek ve 91'i (%68,9) kadındı. Yaş ortalaması 46,4±18,5 ve yaş aralığı 17-86 idi. Hastaların 48'i (%36,4) TB lenfadenit, 23'ü (%17,4) kas iskelet sistemi TB, 17'si (%12,9) dissemine TB, 11'i (%8,3) üriner TB, 11'i (%8,3) abdominal TB, sekizi (%6,1) TB menenjit, altısı (%4,5) plevral TB, beşi (%3,8) genital TB, üçü (%2,3) deri TB idi. Aside dirençli basil pozitifliği; kas-iskelet sistem örneklerinde %21,7, plevral örneklerde %16,6, beyin omirilik sıvısı örneklerinde %12,5, üriner sistem örneklerinde %9 ve lenf nodlarında %6,2 idi. Deri, abdominal ve genital örneklerde ARB saptanmadı. Polimeraz zincir reaksiyon pozitifliği kas-iskelet sistemde %39,1, plevral %33,3, lenf nodunda %26,5, genital %20 idi. Beyin omurilik sıvısı ve deri örneklerinde PZR pozitifliği yoktu. En az bir anti-TB ilaca direnç %20 idi. Mortalite değerlendirilebilen 56 (%42,4) hastanın dokuzunda mortalite gelişti (%16,1).
Sonuç: Lenf bezi TB, hastalarımızda en sık görülen formdu. Ülkemiz verilerine göre plevra TB, EPTB'nin yaygın formlarından biridir. Ancak çalışmanın yapıldığı dönemde hastanemizde plevral biyopsi eksikliğine bağlı plevral EPTB düşük bulunmuştur. Ülkemiz gibi TB'nin endemik görüldüğü bölgelerde klinik bulgularla birlikte ayırıcı tanıda EPTB'nin akılda tutulması ve başta TB kültürü olmak üzere ARB, PZR gibi yöntemlerle tanının doğrulanması önemlidir.
Anahtar Kelimeler: Milier tüberküloz, spondilodiskit, osteomiyelit, epidemiyoloji, çok ilaca dirençli tüberküloz

Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, can involve any organ, primarily the lung, and is an important health problem worldwide, especially in developing countries[1,2]. According to the World Health Organization 2015 global TB report, in line with its "Millenium Development Goals", 43 million lives were saved between 2000 and 2014 with effective diagnosis and treatment of TB. However, 1.5 million people died due to TB in 2014[1]. Despite all measures and therapies, TB continues to be one of the leading global health threats. Extrapulmonary TB (EPTB) is a general term used for clinical forms of TB that do not involve the lungs. Tuberculous involvement of various tissues and organs classified as EPTB can develop years after the primary infection and may present with a rapidly progressive clinical picture[2].

In recent years, the incidence of TB has started to increase again, particularly in developed societies, due to growing numbers of people with human immunodeficiency virus (HIV) infection, leukemia, diabetes, and acquired immune deficiency associated with alcohol and drug abuse[2]. Moreover, higher rates of EPTB in particular have been reported recently in European countries due to the refugee migration crisis[3].

In this study, we evaluated the clinical presentations, acid-fast bacilli (AFB) staining and molecular (polymerase chain reaction/PCR) results of patients with culture-confirmed diagnosis of EPTB in our hospital.

Materials and Methods

Extrapulmonary samples sent to İnönü University, Faculty of Medicine, Department of Microbiology and Clinical Microbiology, Molecular Microbiology Laboratory between January 1, 2004 and December 31, 2014 were analyzed in accordance with the study protocol, and patients in whom *M. tuberculosis* growth was detected were evaluated retrospectively. Patient data were obtained retrospectively from their medical records. Clinical diagnosis of EPTB in our patients was classified as lymph node, musculoskeletal, disseminated, meningitis, urinary, genital, abdominal, cutaneous or pleural, depending on positive culture site[4]. Patients who had only positive sputum culture were not included in the study; however, those suspected of also having miliary involvement were classified as disseminated TB. Musculoskeletal TB was defined as positive spine, joint, and extraspinal osteomyelitis culture. Urinary TB included positive kidney, bladder, and urinary cultures. The genital TB group included males with positive TB cultures of tissue or fluid samples from the prostate, seminal vesicle, epididymis, and testis, and females with positive TB cultures of tissue or fluid samples from the endosalpinges, endometrium, ovaries, and cervix. Abdominal TB was defined as positive TB cultures of peritoneal fluid or abdominal tissue samples such as ileum, ileocecal area, colon, appendix, jejunum, and rectum.

For AFB and culture analyses, each collected sample was first decontaminated and homogenized in an equal volume of NALC-NaOH solution. The samples were vortexed intermittently over a period of 20 minutes at room temperature. Phosphate buffer solution was added to bring the sample volume to 50 ml and the mixture was vortexed again. The sample was centrifuged at 3800 rpm for 20 minutes. After discarding the supernatant, HCl and NaOH were used to adjust the pH of the pellet to 7. When the desired pH was attained, culture and other procedures were performed.

For mycobacterial cultures, 100 µl of the final sample was inoculated into Löwenstein-Jensen (LJ) medium and another 500 µl of the final sample was inoculated into a mycobacteria growth indicator tube (Becton, Dickinson, and Company, Sparks, MD). Another 100 µl of sample was placed on a glass slide for AFB staining, and 1 ml of the sample was reserved for PCR analysis. In our clinical microbiology laboratory, in-house PCR

and a commercially developed PCR kit (COBAS Amplicator *M. tuberculosis* test, Roche Diagnostics, Grenzach-Whylen, Germany) are used together[5]. To prepare the tissues for microscopic evaluation, the samples were paraffin-embedded, sectioned, and deparaffinized, followed by hematoxylin and eosin staining or AFB staining using the Ehrlich-Ziehl-Neelsen method.

Statistical Analysis

Other information about patients with positive TB cultures were obtained by retrospectively reviewing the extracted from hospital's automated medical record system. The results were analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Normally distributed variables were recorded as mean and standard deviation; nonnormally distributed variables were recorded as median and interquartile range. Shapiro-Wilk test was used to assess whether continuous variables within groups were normally distributed. Percent values were given due to the small values in the 2x2 tables.

Results

Of the 132 patients with culture-confirmed EPTB, 41 (31.1%) were male and 91 (68.9%) were female. The mean age was 46.4±18.5 years (18-86 years) while the median age was 49 years. Clinical manifestations included TB lymphadenitis in 48 patients (36.4%), musculoskeletal TB in 23 (17.4%), disseminated TB in 17 (12.9%), urinary TB in 11 (8.2%), abdominal TB in 11 (8.3%), TB meningitis in eight (6.1%), pleural TB in six (4.5%), genital TB in five (3.8%), and cutaneous TB in three patients (2.3%).

Of the affected lymph nodes (n=48), 64.5% (n=31) were cervical, 14.5% (n=7) were supraclavicular, 12.5% (n=6) were submandibular, 4.2% (n=2) were axilary, and 4.2% (n=2) were nasopharyngeal.

Musculoskeletal TB form comprised 17.4% (n=23) of the study group. Of the patients with musculoskeletal TB, 73.9% (n=17) had skeletal involvement and 26.1%(n=6) had muscular involvement. Of the patients with skeletal involvement, 52.9% (n=9) had vertebral involvement, 29.4% (n=5) had paravertebral abscess, 11.8% (n=2) had wrist involvement, and 5.9% (n=1) had femoral involvement. The patients' sex and AFB/PCR distributions according to clinical manifestations are shown in Table 1.

Among the patients who underwent anti-TB drug susceptibility testing, 20% were found to be resistant to at least one drug; isoniazid resistance was detected in 14.5% of the patients, streptomycin resistance in 9.1%, ethambutol resistance in 3.7%, and rifampicin (RIF) resistance in 1.8%. The relationship between anti-TB drug resistance and mortality is shown in Table 2.

Discussion

Since 1980s the AIDS epidemic has been accompanied by a resurgence of TB. Due to the change in disease pattern, extrapulmonary and disseminated forms of the disease have become more common[6-8].

According to 2015 data in the Turkish Fight Against Tuberculosis 2017 report from the Turkish Ministry of Health-General Directorate of Public Health, of 12722 TB patients, 59.5% (n=7,598) had pulmonary TB while 40.5% (n=5,174) had EPTB. Of those with EPTB, 40.9% (n=2,116) were male and 59.1% (n=3,058) were female, and 4.9% (n=626) were reported as disseminated TB[7]. Patients with pulmonary TB were not included in our study. Among our EPTB patients, 31.1% were male, 68.9% were female, and 12.9% had disseminated TB. Human immunodeficiency virus positivity was not detected in any of the patients in our study. This suggests that fewer HIV-positive cases presented to our hospital during the study period.

Mycobacterial culture is the gold standard in the diagnosis of pulmonary and EPTB[2,9]. Results are obtained in 3-8 weeks when culturing in LJ medium and in 5-14 days with automated systems.

Table 1. Clinical and laboratory features of extrapulmonary tuberculosis

	All patients (n=132)	Lymph node TB (n=48)	Musculoskeletal TB (n=23)	Disseminated TB (n=17)	Urinary TB (n=11)	Abdominal TB (n=11)	TB meningitis (n=8)	Pleural TB (n=6)	Genital TB (n=5)	Skin TB (n=3)	Cutaneous TB (n=3)
Sex	91 (68.9)	41 (85.4)	11 (47.8)	11 (64.7)	6 (54.5)	9 (81.8)	7 (87.5)	2 (33.3)	2 (40)	2 (66)	2 (66.6)
Female, n (%)	41 (31.1)	7 (14.5)	12 (52.1)	6 (35.2)	5 (45.5)	2 (18.2)	1 (12.5)	4 (66.6)	3 (60)	1 (33)	1 (33.3)
Male, n (%)											
AFB positive, n (%)	12 (9)	3 (6.2)	5 (21.7)	2 (11.7)	1 (9)	-	1 (12.5)	2 (33.3)	-	-	
PCR positivity, n (%)	29 (21.9)	13 (26.5)	9 (39.1)	3 (17.6)	1 (9)	-	1 (12.5)	2 (33.3)	-	-	

TB: Tuberculosis, AFB: Acid-fast bacillus, PCR: Polymerase chain reaction

Table 2. Comparison of anti-tuberculosis drug resistance according to mortality

	Survivors	Nonsurvivors
Patients with TB strains tested for SM susceptibility		
Susceptible, n (%)	33 (89.2)	4 (10.8)
Resistant, n (%)	2 (66.7)	1 (33.3)
Patients with TB strains tested for INH susceptibility		
Susceptible, n (%)	30 (88.2)	4 (11.8)
Resistant, n (%)	5 (83.3)	1 (16.7)
Patients with TB strains tested for RIF susceptibility		
Susceptible, n (%)	35 (89.7)	4 (10.3)
Resistant, n (%)	0 (0)	1 (100)
Patients with TB strains tested for ETM susceptibility		
Susceptible, n (%)	35 (92.1)	3 (7.9)
Resistant, n (%)	0 (0)	1 (100)
Patients with TB strains resistant to any single drug		
No, n (%)	29 (87.9)	4 (12.1)
Yes, n (%)	6 (85.7)	1 (14.3)
Patients with TB strains resistant to two drugs		
No, n (%)	34 (89.5)	4 (10.5)
Yes, n (%)	1 (50)	1 (50)
Patients with TB strains resistant to four drugs		
No, n (%)	35 (89.7)	4 (10.3)
Yes, n (%)	0 (0)	1 (100)

TB:Tuberculosis, SM: Streptomycin, INH: Isoniazid, RIF: Rifampicin, EMB: Ethambutol

Therefore, in addition to cultures for TB diagnosis, performing staining, PCR, and histopathological analyses of the samples are also important for early diagnosis. However, these methods are less sensitive than mycobacterial culture. While AFB is a rapid and cost-effective method, it has only 60% sensitivity. Moreover, it cannot distinguish *M. tuberculosis* from other mycobacteria. Polymerase chain reaction-based diagnostic tests such as nucleic acid amplification are used to increase the amount of *M. tuberculosis* DNA in the samples. Although this method allows rapid detection in various samples such as blood, urine, and sputum and yields results faster than culture, it is costly and requires advanced laboratory techniques. In addition, its sensitivity is between that of AFB staining and culture.

Culture results are necessary to identify the the mycobacterium in species level and conduct drug susceptibility testing[10]. However, negative results cannot be used to exclude TB because false negativity is common[11]. In the present study, we evaluated patients with definitive positive TB culture, which is the test with the highest diagnostic sensitivity and specificity. However, especially in cases of EPTB, positive cultures may not be easy to achieve. In a series of 6,433 EPTB cases from China, positive culture could only be established in 11% (n=758)[12]. In a systematic review from Turkey that used pooled analysis method to evaluate a total of 694 patients diagnosed with tuberculous lymphadenitis, it was reported that diagnosis was made by AFB staining in 10.6% (51/479) of the cases, by culture in 15.9% (65/408), and by histopathological examination in all of the 648 cases that underwent biopsy[13]. There are studies reporting PCR positivity in 25-65% of the patients with clinically suspected TB lymphadenitis[14,15]. However, the high percentages observed were attributed to the high prevalence of HIV infection. In our study, AFB positivity was highest in musculoskeletal TB with 21.7% (5/23) and PCR positivity was the highest in musculoskeletal TB with 39.1% (9/23), too.

Lymphadenitis is the most common form of EPTB[2]. According to the 2017 Turkey TB report, extrathoracic lymph node (30.2%) and pleural (24.8%) were the most common forms of EPTB involvement[8]. In a study in India, the most frequent clinical manifestation of EPTB in HIV-negative patients was reported as TB lymphadenitis (35%), followed by pleural TB (20%) and musculoskeletal TB (10%)[16]. Of our patients, 36.4% had TB lymphadenitis, with the cervical node being most commonly involved 64.5%. This was followed by musculoskeletal involvement in 17.4%. Vertebrae were the most commonly involved bones (52.9%, 9/17) among patients with skeletal involvement. The frequency of pleural involvement was 4.5%. This relatively low percentage compared with other data from Turkey may be attributable to the low rate of pleural biopsy[8].

In a study from India analyzing genital TB in 110 women over 15 years, AFP positivity was reported in seven cases (6%) and PCR positivity in five cases (4.5%)[17]. In our study, AFP and PCR positivity were not detected in the samples of two women diagnosed with genital TB during evaluation for infertility and ovarian abscess or three men diagnosed as having genital TB during evaluation for inferility and orchitis. This may be due to insufficient and inappropriate sampling.

Cutaneous TB may manifest in various forms, such as lupus vulgaris, TB verrucosa cutis, or scrofuloderma[2]. Different studies report different data regarding the most common form. A study performed in France indicated that scrofuloderma was one of the main clinical forms, while a study conducted in Nepal showed that TB verrucosa cutis was the most common form[18,19]. In a study describing 64 cutaneous TB cases from Turkey, lupus vulgaris was found to be the most common form of cutaneous TB (79.8%), followed by scrofuloderma (15.6%) and TB verrucosa cutis (4.6%)[20]. All of the patients with cutaneous TB in our study were diagnosed as having scrofuloderma.

Resistance to anti-TB drugs is known to be associated with treatment failure and mortality. In 2015, the highest resistance rate observed in TB control dispensaries was to isoniazid, with 13.7% (774/5.648). It was reported that 230 (4.1%) of 5.648 cases who underwent drug susceptibility testing had multidrug-resistant TB (MDR-TB)[8]. Some studies have reported a correlation between mortality and resistance to RIF alone or in combination with other drugs[21]. In our study, 20.0% of the patients who were analyzed for sensitivity to anti-TB drugs were resistant to at least one of them. Resistance to isoniazid was detected in 14.5% of the patients, to streptomycin in 9.1%, to ethambutol in 3.7%, and to RIF in 1.8% of the cases. No significant difference in mortality was detected according to single or MDR in our patients. However, the retrospective nature of the study limited the evaluation of mortality and drug resistance pattern in all patients.

Conclusion

In EPTB, the nonspecific clinical signs and symptoms as well as inadequate diagnostic tools may make it difficult to establish a diagnosis. The collection of appropriate clinical samples, primarily for culture, and early initiation of treatment are crucial for diagnosis and treatment success in patients with suspected EPTB.

Ethics

Ethics Committee Approval: The study was approved by the İnönü University of Ethics Committee (protocol number: 201-100).

Informed Consent: Since this was a retrospective study no informed consent was received.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A.T., Ü.K., B.O., Y.B., Y.E., F.M., Concept: S.A.T., Ü.K., Design: S.A.T., Ü.K., Data Collection or Processing: S.A.T., Analysis or Interpretation: S.A.T., Literature Search: S.A.T., Ü.K., Writing: S.A.T.

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