

Mycobacterium tuberculosis Infections in HIV-infected Patients

HIV ile İnfekte Hastalarda *Mycobacterium tuberculosis* İnfeksiyonları

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ABSTRACT

Introduction: Tuberculosis (TB) still continues to be the leading cause of death for Human Immunodeficiency Virus (HIV) infected patients, and it accounts for approximately one of three acquired immunodeficiency syndrome (AIDS) related deaths. The study aimed to analyze clinical and laboratory data of *Mycobacterium tuberculosis* infection in HIV infected patients.

Materials and Methods: Medical records of adult (aged ≥ 18 years) HIV infected patients diagnosed and under medical care between January 2005 and November 2018 were obtained and analyzed retrospectively by searching hospital database system.

Results: Fifteen patients (4.5%) had TB among the 336 HIV infected patients. There was no statistically significant difference between the age of HIV-infected patients with and without TB disease (38.07 ± 8.48 vs 39.26 ± 11.67 ; $p: 0.697$). Diagnosis of TB disease and HIV infection were concurrent during presentation in 9 (60%) patients, while six (40%) patients had a previous history of HIV infection and treatment. Five (83.3%) of 6 patients receiving antiretroviral therapy (ART) had no viral suppression due to non-adherence. Median CD4 T lymphocyte count was $114/\text{mm}^3$ (0-436) at the time of TB diagnosis whereas it was $408/\text{mm}^3$ (1-1734) in those without TB disease at the time of initial HIV infection diagnosis, and the difference was statistically significant ($p < 0.05$). Odds ratio for CD4 T lymphocyte count less than 200 in HIV infected patients with TB disease was 14.89 (confidence interval 95%: 4.08-54.34). While ten (66.7%) patients had pulmonary involvement, five (33.3%) patients had extrapulmonary involvement. There was no statistically significant difference between the median CD4 T lymphocyte counts of patients with pulmonary involvement ($107/\text{mm}^3$, range:0-436) and extrapulmonary involvement ($140/\text{mm}^3$, range: 86-259) ($p= 0.391$).

Conclusion: Tuberculosis disease should be considered in patients who have applied at advanced stages of HIV infection or whose virological suppression could not be achieved due to incompatibility with ART treatment.

Key Words: HIV; AIDS; Tuberculosis; CD4

ÖZ

HIV ile İnfekte Hastalarda *Mycobacterium tuberculosis* İnfeksiyonlarıHeval Can BİLEK¹, Aydın DEVECİ¹, Esra TANYEL¹¹ Ondokuz Mayıs Üniversitesi Tıp Fakültesi Hastanesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Samsun, Türkiye

Giriş: Tüberküloz (TB), İnsan immün yetmezlik virüsü (Human immunodeficiency virus: HIV) ile infekte hastalarda önde gelen ölüm nedeni olmaya devam etmekte olup, kazanılmış immün yetmezlik sendromu (Acquired immunodeficiency syndrome: AIDS) ile ilgili her üç ölümden yaklaşık birinin nedenini oluşturmaktadır. Bu çalışmada HIV ile infekte hastalarda gelişen TB hastalığının klinik ve laboratuvar verilerinin irdelenmesi amaçlandı.

Materyal ve Metod: Ocak 2005 ve Kasım 2018 tarihleri arasında HIV tanı ve tedavisi alan 18 yaş ve üzerindeki hastalar çalışmaya dahil edildi. Hastaların verileri hastane otomasyon kayıt sistemi taranarak retrospektif olarak elde edildi.

Bulgular: Çalışma döneminde 336 HIV ile infekte hasta tespit edildi. Hastaların 15'inde (%4.5) TB hastalığı saptandı. TB hastalığı olan ve olmayan HIV ile infekte hastaların yaş ortalaması (38.07 ± 8.48 vs 39.26 ± 11.67) arasında istatistiksel olarak anlamlı bir fark yoktu ($p:0.697$). TB hastalığı tanısı, dokuz (%60) hastada HIV enfeksiyonu tanısı aldığı anda konulurken, altı (%40) hastada ise daha önceden HIV enfeksiyonu ve tedavisi öyküsü vardı. Antiretroviral tedavi (ART) deneyimli olan beş hastada tedavi uyumsuzluğu nedeniyle viral baskılanma sağlanmamıştı. TB hastalığı olan HIV ile infekte hastalarda TB tanısı sırasında ortanca CD4 T lenfosit sayısı $108/\text{mm}^3$ (0-436); TB hastalığı olmayanlarda HIV enfeksiyonunun tanısı sırasında ise $408/\text{mm}^3$ (1-1734) olarak belirlendi ve aradaki fark istatistiksel açıdan anlamlıydı ($p < 0.05$). TB hastalığı olan HIV ile infekte hastalarda CD4 T lenfosit sayısının $200/\text{mm}^3$ 'ün altında olma Odds oranı 14.89'du (%95 güven aralığı: 4.08-54,34). Hastaların onunda (%66.7) akciğer tutulumu mevcutken beş (%33.3) hastada ise ekstrapulmoner tutulum mevcuttu. Akciğer tutulumu olan hastalar medyan CD4 T lenfosit sayısı $107/\text{mm}^3$ (0-436) iken ekstrapulmoner tutulumu olan hastalarda ise $140/\text{mm}^3$ 'tü (86-259) ve her iki grup arasında istatistiksel açıdan anlamlı bir fark yoktu ($p = 0.391$).

Sonuç: HIV enfeksiyonunun ilerlemiş evrelerinde başvuran veya ART tedavisine uyumsuzluk nedeni ile virolojik baskılanma sağlanamamış hastalarda tüberküloz hastalığı göz önünde bulundurulmalıdır.

Anahtar Kelimeler: HIV; AIDS; Tüberküloz; CD4

INTRODUCTION

Tuberculosis (TB) remains the leading cause of death in patients infected with the Human Immunodeficiency Virus (HIV). It accounts for about one of three deaths related to Acquired Immunodeficiency Syndrome (AIDS). It is estimated that approximately 9% of 10 million people who developed TB disease in 2017 are infected with HIV^[1]. Both TB and HIV can neutralize the host's immune system responses through mechanisms that are not fully understood. HIV co-infection is the most substantial known risk factor for the progression of TB infection to active disease and increases the risk of latent TB reactivation by 20 times^[2,3]. Likewise, TB aggravates the clinical course of HIV infection and complicates antiretroviral therapy (ART)^[4,5]. We aimed to evaluate the prevalence of tuberculosis disease in HIV-infected patients, clinical types of disease, and immunological status of the patients.

MATERIALS AND METHODS

Medical records of adult (aged ≥ 18 years) HIV-infected patients diagnosed and under medical care at Ondokuz Mayıs University Research and Education Hospital between January 2005 and November 2018 were analyzed retrospectively by searching hospital database system. HIV infection was defined by the detection of HIV 1/2 antigen/antibodies by the electrochemiluminescence immunoassay method (Cobas e411, Roche Diagnostics) and validation of samples in a public health laboratory by a descriptive method (Western blot, line immunoassay or indirect immunofluorescence). Viral load and CD4 T lymphocyte cell count of the patients were determined by real-time polymerase chain reaction (PCR) and peripheral blood analysis by flow cytometer method, respectively.

TB diagnosis was based on *M. tuberculosis* growth or positive molecular diagnostic tests (polymerase chain reaction; PCR) in clinical samples

or clinical (coughing for longer than three weeks, fatigue, fever) and radiological findings (cavitary lesions, pleural effusion, miliary pattern, hilar lymphadenopathy) consistent with TB. Mann Whitney U test and Student t-tests were used to analyze parametric data by using SPSS Statistics 21.0 software. Odds ratio was calculated for risk determination of CD4 T lymphocyte count. The study was approved by Ondokuz Mayıs University Clinical Research Ethics Committee on 19.11.2019 with the decision number of 2019/720.

RESULTS

It was determined that a total of 336 HIV-infected patients, including 52 (15.4%) females and 284 (84.6%) males, were diagnosed and under medical care during the study period. Anti-tuberculosis therapy was initiated in 15 (4.5%) of these patients due to TB disease.

All patients diagnosed with TB disease were males. The mean age of HIV infected patients without TB disease was 39.26 ± 11.67 years whereas the mean age of patients with TB disease was 38.07 ± 8.48 years. There was no statistically significant difference between the two groups ($p= 0.697$).

Nine (60%) patients were diagnosed with TB disease concurrent with initial HIV infection diagnosis and, six (40%) patients were ART experienced patients due to earlier diagnosis of HIV infection. Virological suppression (HIV-RNA <50 copies/mL) was achieved in one (17%) patient on ART whereas the remaining 5 (83%) patients did not have viral suppression due to nonadherence to ART.

Median CD4 T lymphocyte count was $114/\text{mm}^3$ (0-436) at the time of TB diagnosis, whereas it was $408/\text{mm}^3$ (1-1734) in those without

TB disease at the time of initial HIV infection diagnosis and the difference was statistically significant ($p < 0.05$) (Table 1). Odds ratio for CD4 T lymphocyte count less than 200 in HIV infected patients with TB disease was 14.89 (confidence interval 95%: 4.08-54.34).

It was determined that there was isolation of *M. tuberculosis* in nine (60%) of fifteen patients; tuberculosis PCR positivity in six (50%) of twelve patients; positive acid-fast bacilli (AFB) on direct microscopic examination in 8 (50%) of fifteen patients (Table 2). Computerized tomography (CT) imaging revealed micronodules in nine (60%) patients; mediastinal lymphadenopathy in nine (60%) patients; cavitary nodules in five (33.3%) patients; pleural effusion and pleural thickening in two (13.3%) patients; conglomerate lymph nodes in two (13.3%) patients; and meningeal involvement in 1 (6.7%) patient. All patients had at least one abnormal finding in CT imaging.

While 10 (66.7%) patients had pulmonary involvement, five (33.3%) patients had extrapulmonary involvement including two (13.3%) pleurisy, one (6.7%) miliary, one (6.7%) lymphadenitis and one (6.7%) central nervous system involvement (Table 2). Median CD4 T lymphocyte counts of the patients with pulmonary involvement was $107/\text{mm}^3$ (0-436), whereas it was $140/\text{mm}^3$ (86-259) in patients with extrapulmonary involvement ($p= 0.391$).

Antituberculosis induction therapy including isoniazid, rifampicin, pyrazinamide and ethambutol were used for thirteen (86.7%) patients for two months and followed by maintenance therapy including isoniazid and rifampicin for 10 months. Remaining two (13.3%) patients were treated by rifabutin instead of rifampicin due to potential drug interaction with ART regime including a

Table 1. Characteristics and CD4 T lymphocyte median counts of HIV infected patients with and without TB disease

	With TB Disease	Without TB disease	p
Number of patients			
Female	0 (0)	52 (15.4%)	
Male	15 (4.5%)	269 (80.1%)	
Age (years)	38.1 ± 8.5	39.3 ± 11.7	0.697
CD4 T lymphocyte count (Median)	$114/\text{mm}^3$ (0-436)	$408/\text{mm}^3$ (1-1734)	< 0.05

protease inhibitor. Dolutegravir dose was increased to 2x50 mg during antituberculosis treatment. 13 (86.7%) patients recovered while two (13.3%) patients died. Antituberculosis and ART regimes, adverse events, coinfections and outcome are summarized in Table 2.

DISCUSSION

It is estimated that one-third of the world population is latently infected with *M. tuberculosis*^[6]. Approximately 10% of individuals infected with *M. tuberculosis* develop clinical disease mainly resulting from reactivation or post-primary TB^[7]. Therefore, while the risk of developing active TB in immunocompetent adults is 5-10% throughout their lifetime, this risk increases annually between 5-15% in HIV-infected individuals^[8]. The prevalence of TB-HIV co-infection varies in different geographic regions; HIV prevalence in TB patients was reported to be 3.8-72.3%, while TB prevalence in HIV-infected patients was reported as 2.9-64.5%^[9]. Global tuberculosis report of the World Health Organization (WHO) reported that HIV prevalence in newly diagnosed and recurrent tuberculosis cases was 0-4.9% in Turkey^[10]. The prevalence of tuberculosis was found 4.5% among 1475 HIV-infected patients in an earlier study in Turkey^[11]. Similarly, our study determined that the prevalence of tuberculosis in HIV-infected patients was 4.5%.

In our study, the CD4 T lymphocyte median count of patients without tuberculosis disease was 408/mm³, whereas the CD4 T lymphocyte median count of patients with tuberculosis disease was less than 200/mm³ (114/mm³) that is considered as severe immunosuppression. High Odds ratio for low CD4 T lymphocyte count (<200/mm³) in HIV infected patients with TB disease showed increased risk of TB disease among patients with low CD4 T lymphocyte count. One of the key features of AIDS is depletion of CD4 T lymphocytes that contributes significantly to the increased risk of reactivation of latent TB and predisposition to new tuberculosis infection. HIV has also been shown to disrupt apoptotic response of tumor necrosis factor (TNF) mediated macrophage and consequently facilitating bacterial survival^[12]. Median CD4 T lymphocyte count of HIV-infected patients with TB disease was lower than patients without TB (p< 0.05).

Extrapulmonary tuberculosis (EPTB) is defined as TB disease that affects tissues and organs outside the pulmonary parenchyma, and the incidence of EPTB worldwide in 2016 was reported to be 15%^[10]. EPTB forms including pleural effusion, meningitis, lymphadenitis and pericardial disease are more common in HIV-infected patients, and it occurs in 70% of people with CD4 T lymphocyte count less than 100/mm³ and approximately 30% of people with CD4 T lymphocyte count above 300 cells/mm³^[13,14]. EPTB was determined in 33.3% of the patients with TB in our study.

The most common TB diagnostic method includes microscopic examination of the stained sputum for AFB^[15]. Microscopy has the advantage of being cheap with acceptable specificity and relatively faster diagnostic test. However, clinical specimen must contain approximately ten mycobacteria per milliliter to be effective in staining^[16]. The sensitivity of sputum microscopy in HIV infection ranges from 43-51%^[17]. Isolation of *M. tuberculosis* is much more sensitive than microscopy in the diagnosis of TB disease among HIV-infected patients^[18]. Compared with microscopic evaluation, nucleic acid amplification tests (NAAT) have a better positive predictive value in both microscopic positive and negative samples^[19,20]. In addition, NAAT provides faster results than the isolation of mycobacteria in culture that requires several weeks for isolation. Despite the obvious advantages of NAAT compared to conventional diagnostic tests, their use is limited in tuberculosis-endemic environments due to high cost and requirement of special equipment^[21]. NAAT could only be studied from the clinical samples of twelve of sixteen HIV-infected tuberculosis patients, and 50% were found to be positive. Although tuberculosis culturing yielded late results compared to NAAT, the fact that it is possible to work continuously in the laboratory, requires less technical opportunities, and the rate of isolation in our study was higher than NAAT, supports its diagnostic importance.

At advanced levels of immune suppression, 20% of HIV-infected patients with TB disease are estimated to have normal chest radiographs; however, CT assessment of such patients often shows subtle abnormalities, including small no-

Table 2. Diagnostic procedures, treatment regimes and outcome of patients

Patients	Involvement	Co-infection	Positive Diagnostic Test		ART Status	Anti-TBC	ART	Adverse Events	Outcome
Patient 1	Lung	No	Culture, ARB	Culture, ARB	Experienced	H-R-Z-E	TDF-FTC-EFV	No	Recovered
Patient 2	Lung	Cryptococcosis	CT imaging	CT imaging	Experienced	H-R-Z-E	TDF-FTC-DTG	No	Exitus
Patient 3	Lung	Syphilis	Culture, ARB, NAAT	Culture, ARB, NAAT	Experienced	H-R-Z-E	TDF-FTC-DTG	No	Recovered
Patient 4	Lung	Syphilis, HPV	Culture, ARB, NAAT	Culture, ARB, NAAT	Experienced	H-R-Z-E	ABC-3TC-DTG	No	Recovered
Patient 5	Lymph node	No	ARB, NAAT	ARB, NAAT	Experienced	H-RBT-Z-E	TDF-FTC-LPV/r	Muscle and joint pain	Recovered
Patient 6	CNS	PCP	Culture, NAAT	Culture, NAAT	Experienced	H-R-Z-E	TDF-FTC-DTG	No	Recovered
Patient 7	Lung	No	Culture, ARB, NAAT	Culture, ARB, NAAT	Naive	H-R-Z-E	ABC-3TC-DTG	No	Recovered
Patient 8	Lung	No	Culture and ARB	Culture and ARB	Naive	H-R-Z-E	TDF-FTC-DTG	No	Recovered
Patient 9	Lung	No	Culture, ARB, NAAT	Culture, ARB, NAAT	Naive	H-R-Z-E	TDF-FTC-DTG	Nausea-vomiting	Recovered
Patient 10	Lung	PCP, Candidiasis	Culture, ARB	Culture, ARB	Naive	H-R-Z-E	TDF-FTC-EFV	Transaminase and uric acid elevation	Recovered
Patient 11	Lung	PCP, Syphilis, Cryptosporadiazis	CT imaging	CT imaging	Naive	H-R-Z-E	AZT-3TC-EFV	No	Recovered
Patient 12	Lung	Toxoplasmosis, candidiasis	CT imaging	CT imaging	Naive	H-R-Z-E	TDF-FTC-EFV	No	Exitus
Patient 13	Miliary	No	Culture	Culture	Naive	H-R-Z-E	TDF-FTC-DTG	IRIS, transaminase elevation	Recovered
Patient 14	Pleura	No	ADA, CT imaging	ADA, CT imaging	Naive	H-R-Z-E	ABC-3TC-DTG	No	Recovered
Patient 15	Pleura	No	ADA, CT imaging	ADA, CT imaging	Naive	H-RBT-Z-E	TDF-FTC-LPV/r	No	Recovered

ABC: Abacavir, ADA: Adenosine deaminase, ARB: Acid fast bacilli, ART: Antiretroviral therapy, AZT: Zidovudine, CNS: Central nervous system, CT: Computerized tomography, DTG: Dolutegravir, E: Ethambutol, EFV: Efavirenz, FTC: Emtricitabine, H: Isoniazid, HPV: Human papilloma virus, IRIS: immune reconstitution inflammatory syndrome, LPV/r: Lopinavir/ritonavir, NAAT: Nucleic acid amplification tests, PCP: *Pneumocystis jirovecii* pneumonia, R: Rifampicin, RBT: Rfabutrin, TDF: Tenofovir disoproxil, Z: Pyrazinamide, 3TC: Lamivudine.

dules and lymph node enlargement^[22,23]. After the diagnosis of EPTB, the relationship with pulmonary TB should always be investigated, as they can coexist. Although the treatment basis is the same, the contagious nature of pulmonary TB requires some additional tests that need to be done^[24,25]. In our study, chest CT findings were found to be very supportive in terms of diagnosis, since the lung is the primary focus for TB infection or the source tissue for the spread of the infection to other tissues.

Our study has some limitations; first it is a retrospective study, and data collection is based on automated database, therefore there were lack of some information regarding socioeconomic status of patients, diagnostic procedures and adverse events. Gold standard diagnostic test was positive in nine of the fifteen patients and remaining six patients were diagnosed according to clinical, radiological and biochemical findings. Small sample size is another limitation of the study.

In our study, it was determined that low CD4 T lymphocyte count is the main factor in the emergence of TB disease. TB disease should not only be considered in patients admitted at advanced stages of HIV infection but also in patients who are non-adherent to the ART treatment. However, the diagnostic gold standard for active TB is isolation of bacteria by culture or molecular methods in HIV-infected people, patients with typical clinical signs may be diagnosed by using CT imaging in the absence of bacterial isolation.

ETHICS COMMITTEE APPROVAL

The ethical approval for this study was obtained from Ondokuz Mayıs University Clinical Research Ethics Committee (Decision no: B.30.2.ODM.0.20.08/820-887, Date: 19.11.2019).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: AD, HCB, ET

Analysis/Interpretation: HCB, AD, ET

Data Acquisition: HCB, AD, ET

Writing: HCB, AD, ET

Revision and Correction: HCB, AD, ET

Final Approval: HCB, AD, ET

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