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RESEARCH ARTICLE
KLİNİK ÇALIŞMA

Coexistence of tuberculosis and COVID-19 pneumonia: A presentation of 16 patients from Turkey with their clinical features

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ABSTRACT

Coexistence of tuberculosis and COVID-19 pneumonia: A presentation of 16 patients from Turkey with their clinical features

Introduction: Coronavirus disease 2019 (COVID-19) and tuberculosis are serious and mortal diseases worldwide. There are few studies about the association between tuberculosis and COVID-19 pneumonia. We aimed to describe the characteristics of tuberculosis and COVID-19 co-infection cases in light of the literature.

Materials and Methods: Tuberculosis patients who applied to the tuberculosis outpatient clinic between September 1-September 30, 2020, and patients hospitalized in the COVID-19 service between June 1- September 30, 2020, were retrospectively screened. Patients with tuberculosis and COVID-19 co-infection were recorded. Clinical, radiological, laboratory data, and treatments were recorded and analyzed. For the diagnosis of tuberculosis, sputum acid-resistant bacillus (ARB) smear or culture positivity or pathological diagnosis were used. For the diagnosis of COVID-19, positive real-time reverse transcription-polymerase chain reaction and/or typical radiological findings were sought.

Results: Seven hundred and fifty-one patients' data at the tuberculosis outpatient clinic, 229 patients' data at the COVID-19 clinic were screened. Sixteen patients meet the criteria. COVID-19 infection rate in tuberculosis patients was 2.1%. Sixty-nine percent of the patients had received COVID-19 disease during diagnosis or initial tuberculosis treatment phase. There were no drug-drug interactions between anti-tuberculosis drugs and COVID-19 treatment. During the COVID-19 treatment, one patient (6%) died, 15 (94%) patients completed the treatment.

Conclusion: In our study, no effect of the coexistence of TB and COVID-19 on morbidity or mortality was observed. Although the number of patients is small, it can be said that patients with early TB disease and with widespread involvement may be riskier for COVID-19 infection. Frequent hospital visits by TB patients may be a risk for COVID-19. It may be beneficial to carry out the

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diagnosis and treatment of tuberculosis patients by tuberculosis dispensaries as in our country or authorized units to reduce the risk of hospital admissions and COVID-19 transmission.

Key words: COVID-19; infection; pandemic; tuberculosis

ÖZ

Tüberküloz ve COVID-19 pnömonisi birlikteliği: Türkiye'den 16 hastanın klinik özellikleri ile sunumu

Giriş: Koronavirüs hastalığı 2019 (COVID-19) ve tüberküloz tüm dünyayı etkileyen ciddi ve ölümcül hastalıklardır. Tüberküloz ve COVID-19 pnömonisinin birlikteliği hakkında az sayıda çalışma vardır. Tüberküloz ve COVID-19 koenfeksiyon olgularının literatür eşliğinde sunulması amaçlanmıştır.

Materyal ve Metod: Hastanemiz Tüberküloz polikliniğine 1 Eylül 2020-30 Eylül 2020 tarihlerinde başvuran tüberküloz hastaları ile, 1 Haziran 2020-30 Eylül 2020 tarihlerinde COVID-19 servisinde yatan hastalar retrospektif olarak tarandı. Tüberküloz ve COVID-19 koenfeksiyonu olan vakalar kayıt altına alındı. Hastaların klinik, radyolojik, laboratuvar verileri, tedavileri kaydedildi ve analiz edildi. Tüberküloz tanısı için balgam aside dirençli basil (ARB) yayması veya kültür pozitifliği veya patolojik tanı kullanıldı. COVID-19 tanısı için pozitif gerçek zamanlı ters transkripsiyon-polimeraz zincir reaksiyonu ve/veya tipik radyolojik bulgular arandı.

Bulgular: Tüberküloz polikliniğindeki 751 hastanın, COVID-19 kliniğindeki 229 hastanın verileri tarandı. On altı hasta kriterleri karşılıyordu. Tüberküloz hastalarında COVID-19 enfeksiyon oranı %2.1 olarak saptandı. Hastaların %69'u COVID-19 tanısını tüberküloz tanısı ile beraber ya da tüberküloz tedavisinin inisiyal faz döneminde aldı. Anti-tüberküloz ilaçlar ile COVID-19 tedavisi arasında ilaç-ilaç etkileşimi saptanmadı. COVID-19 tedavisi sırasında bir hasta (%6) öldü, 15 (%94) hasta tedaviyi tamamladı.

Sonuç: Çalışmamızda, tüberküloz ve COVID-19 birlikteliğinin, morbidite ve mortaliteye etkisi gözlenmedi. Hasta sayısı az olsa da, tüberküloz tedavisinin erken döneminde olmak ve yaygın tutulumun olmasının, COVID-19 enfeksiyonu için risk oluşturabileceği söylenebilir. Tüberküloz hastalarının sık hastane başvurusu da, COVID-19 için risk oluşturabilir. Hastane başvurusu ve COVID-19 bulaşma riskini azaltmak için, tüberküloz hastalarının tanı ve tedavisinin ülkemizde olduğu gibi Verem Savaş Dispanserleri veya yetkili birimler tarafından yapılması faydalı olabilir.

Anahtar kelimeler: Enfeksiyon; COVID-19; pandemi; tüberküloz

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has become a pandemic since first detected in Wuhan, China, in December 2019. World Health Organization (WHO) reported 34.804.348 confirmed cases and 1.030.738 deaths by October 6, 2020 and the number increases day by day (1). Tuberculosis (TB) is a severe and mortal disease, especially in developing countries. In 2018, it infected 10.0 million people, and 1.2 million TB patients died (2).

Chronic kidney diseases, diabetes, malignancy, chronic obstructive lung diseases (COPD) are both risk factors for COVID-19 (3). These diseases are also risk factors for TB (4). Symptoms like fever, cough, fatigue, dyspnea are mostly seen in both diseases (5).

Limited studies have investigated COVID-19 and TB, which are important health problems for the whole world. We aimed to present the general characteristics and treatment course of patients diagnosed with COVID-19 among TB patients who applied to our hospital in light of the literature.

MATERIALS and METHODS

It was a retrospective study that included TB patients, admitted to our hospital between September 1-September 30, 2020, and COVID-19 patients who got treatment at the clinic between June 1-September 30, 2020. Ethical approval for this study was obtained from the Ethics Committee of our institutional board (decision number: 2020-46, decision date: 5.11.2020) and the Ministry of Health.

Within the specified period, all patients admitted to the TB outpatient clinic and hospitalized in the COVID-19 clinic were screened, and patients with coexistence with TB and COVID-19 were recorded. Demographic characteristics, radiological and laboratory data, the treatments given, and the treatment results were recorded. For the diagnosis of TB, sputum acid-resistant bacillus (ARB) smear or culture positivity or pathological diagnosis were used. For the diagnosis of COVID-19, positive real-time reverse transcription-polymerase chain reaction (RT-PCR) and/or typical radiological findings (bilateral ground-glass opacities, consolidation, vascular enlargement, etc.) were sought (6). Patients with active tuberculosis

or whose treatment was recently terminated were excluded from the study.

Statistical analysis was performed using SPSS version IBM Statistic 21.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, mean \pm SD in continuous variables and median (min-max) values were given using nonparametric tests for data that did not show normal distribution. Descriptive statistics of categorical data are presented as numbers and percentages (%).

RESULTS

In the mentioned period, 751 patients' data at TB outpatient clinic and 229 patients' data at COVID clinic were screened. Sixteen patients met the criteria of having TB and COVID-19 together. COVID-19 infection rate in TB patients was 2.1%. Five patients (31%) were males, and 11 (68.7%) were females. Mean age was 40.68 ± 17.63 STD (min 16-max 88). One patient was African, and one was Syrian; other patients were Turkish (87.5%). Two patients were current smokers (12.5%), one was an ex-smoker (6.2%), and the others (81.2%) were nonsmokers. Two patients (12.5%) had asthma, two had (12.5%) cardiac diseases, two patients (12.5%) had diabetes. Eleven patients (68.7%) had no chronic diseases that may lead to the TB or COVID-19 infection and HIV was not detected in any patient. Data on patients' symptoms and tuberculosis disease are summarized in Table 1. For the diagnosis of COVID-19, at laboratory findings; two patients (12.5%) had leukocytosis, one patient (6%) had anemia, neutrophil count was high at two patients (12.5%), seven patients (43.7%) had lymphopenia, neutrophil/lymphocyte rate was ≥ 4 at four patients (25%), liver function tests were high at five patients (31%), D-dimer was >0.5 mg/L at six patients (6/11) (54.5%) and fibrinogen was >400 mg/dL at seven patients (7/11) (64%). Thirteen patients (86.6%) had isoniazid, rifampicin, pyrazinamide, and ethambutol; one patient (6.2%) had isoniazid, rifampicin, prazinaamide and streptomycin, one patient (6.2%) had isoniazid, rifampicin, ethambutol and streptomycin treatment.

During the COVID-19 diagnosis, 11 (69%) patients had symptoms (cough, fever, fatigue, headache) about COVID-19 disease. In 12 patients who had thorax computed tomography (CT), nine (75%) patients had ground-glass opacities and all had bilateral involvement (Figure 1). Radiological findings at the onset of TB infection and COVID-19 infection were summarized in Table 2. All patients with normal

Table 1. Patients' symptoms and data on tuberculosis (TB) disease

Symptoms	
No symptoms	4 (25%)
Dyspnea	3 (18.7%)
Anorexia	4 (25%)
Fatigue	5 (31.2%)
Sputum	2 (12.5%)
Cough	7 (43.7%)
Nausea-vomiting	1 (6.2%)
Fever	3 (18.7%)
Hemoptysis	1 (6.2%)
Skin rash	1 (6.2%)
Previous history of TB	
Yes	3 (19%)
No	13 (81%)
Active tuberculosis	15 (94%)
Sequela tuberculosis	1 (6%)
TB site	
Pulmonary	9 (60%)
Extrapulmonary	5 (33%)
Pulmonary+Extrapulmonary	1 (7%)
Site of extrapulmonary TB	
Lymphadenitis	3 (50%)
Pleural	1 (17%)
Lymphadenitis+Pleural	2 (33%)
Microbiological findings	
Sputum smear-positive	8/14 (57%)
Sputum smear-negative	6/14 (43%)
Sputum culture positive	9/14 (one culture ongoing) (64%)
Drug resistance	
Yes	2 (14%)
No	12 (86%)

radiology at the beginning of COVID-19 infection had extrapulmonary tuberculosis. Of these patients, two had normal radiology at the beginning of TB infection and one had pleural effusion. In four of the eight patients with unilateral TB infection, bilateral radiological involvement was detected at the onset of COVID-19. While unilateral involvement was observed in two patients, thorax CT was normal in one patient and CT was not performed in one patient. All TB cases who had bilateral involvement had bilateral ground-glass opacities at the beginning of COVID-19 infection.

Ten (62.5%) patients had positive RT-PCR. Data related to the patients who received the diagnosis of COVID-19 at which time of TB treatment is given in Table 3. While four patients (25%) were simultaneously diagnosed with TB and COVID-19, seven



Figure 1. Bilateral ground-glass areas due to COVID-19 pneumonia and cavitary lesion in the right upper lobe detected in 3-4 months of tuberculosis treatment in a 32-year-old female patient.

Table 2. Radiological findings

	At the onset of tuberculosis infection	At the onset of COVID-19 infection (n= 15)
Radiological involvement		
Normal	2 (12.5%)	3 (20%)
Unilateral	8 (50%)	2 (13%)
Bilateral	6 (37.5%)	10 (67%)
Radiological pattern		
Infiltration	6 (43%)	2 (17%)
Cavitary+infiltration	4 (28.5%)	
Effusion	3 (21.5%)	1 (8%)
Nodule	1 (7%)	
Ground-glass opacities (GGO)	-	2 (17%)
GGO+infiltration	-	3 (25%)
GGO+cavitary	-	1 (8%)
GGO+infiltration+cavitary	-	3 (25%)
Involvement site at Chest X-ray		
RUZ¶	6 (43%)	4 (33%)
RMZ*	6 (43%)	8 (67%)
RLZ**	7 (50%)	10 (83%)
LUZ‡	1 (7%)	1 (8%)
LMZ1	3 (21%)	2 (17%)
LLZ#	11 (79%)	11 (92%)
Involvement site at Thorax-CT (n= 12)		n= 12
RUL ^δ	6 (50%)	5 (42%)
RML ^φ	5 (42%)	8 (67%)
RLL ^φ	6 (50%)	9 (75%)
LUL‡	1 (8%)	4 (33%)
Lingula	4 (33%)	5 (42%)
LLL~	1 (8%)	10 (83%)

RUZ¶: Right upper zone, RMZ*: Right middle zone, RLZ**: Right lower zone, LUZ‡: Left upper zone, LMZ1: Left middle zone, LLZ#: Left lower zone, RUL^δ: Right upper lobe, RML^φ: Right middle lobe, RLL^φ: Right lower lobe, LUL‡: Left upper lobe, LLL~: Left lower lobe.

Table 3. Timing of COVID-19 diagnosis during tuberculosis (TB) treatment

TB treatment time	
1-2 months	7 (44%)
3-4 months	3 (19%)
5-6 months	0
6-9 months	1 (6%)
After TB treatment	1 (6%)
TB and COVID-19 diagnosed at the same time	4 (25%)

patients (44%) were diagnosed with COVID-19 in the first two months of TB treatment. In other words, the majority of patients got COVID-19 in the first period of TB treatment.

Ten (62.5%) patients were treated in the hospital, and mean hospital stay was 6.1 ± 2 STD days (median:5; min-max: 5-12 days). Ten (62.5%) patients received hydroxychloroquine, eight (50%) patients received favipiravir, eight (50%) patients received anticoagu-

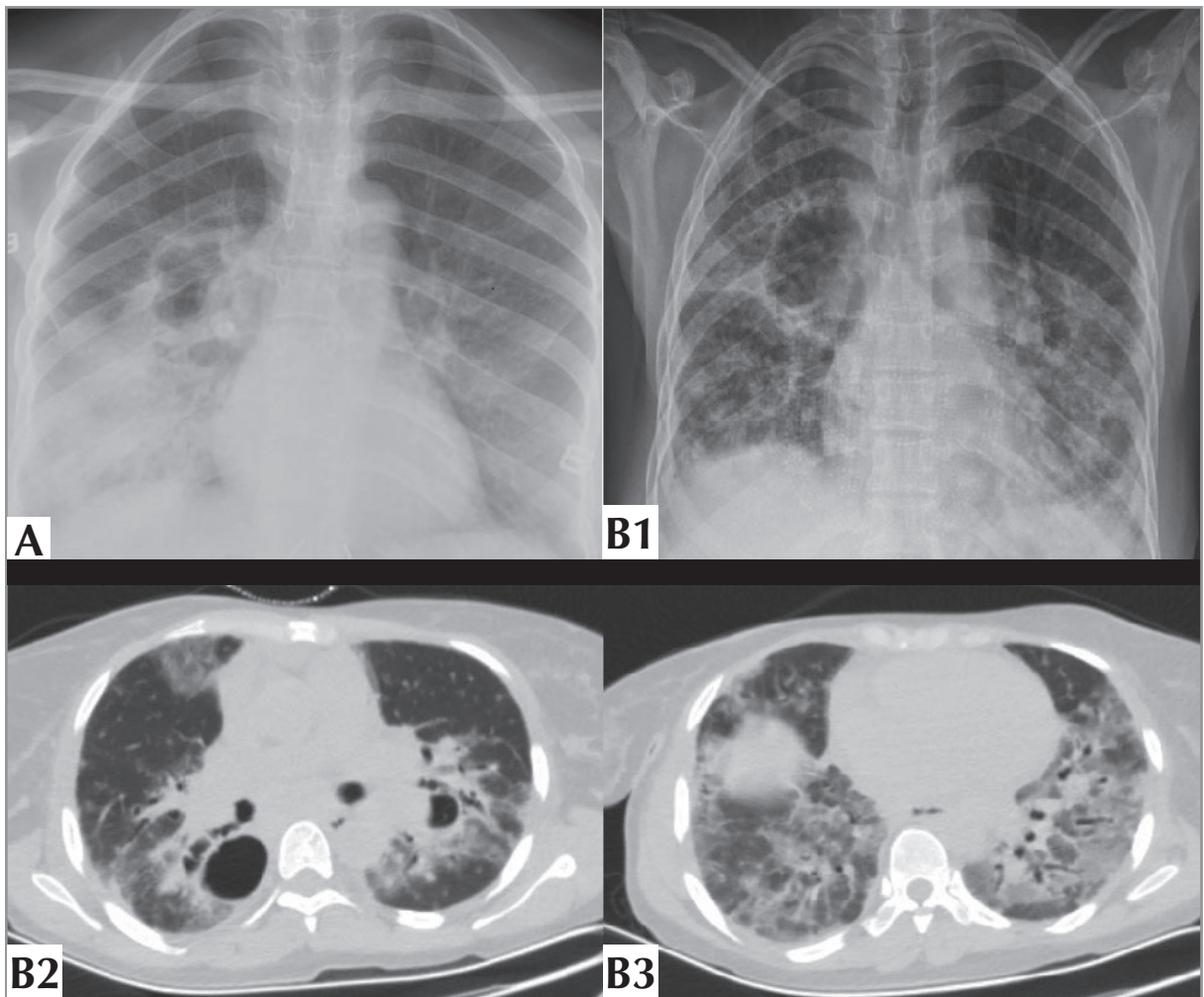


Figure 2. A. Chest X-ray at the beginning of tuberculosis diagnosis **B1, B2, B3-** Chest X-ray and Thorax CT at the beginning of COVID 19 diagnosis.

lant, five (31%) patients need O₂ treatment, four (25%) patients received C vitamin, one (6%) patient received methylprednisolone, six (37.5%) patients received nonspecific antibiotic treatment. The time between the diagnosis of TB and the diagnosis of COVID-19 in patients receiving active TB treatment was 68.2 ± 65.9 STD days (min: 11- max: 270 days). During COVID-19 treatment, one patient (6%) died, other 15 (94%) patients completed the treatment. The patient who died was a 40-year-old African female who had active lung tuberculosis without any additional disease (Figure 2). Among the patients who had tuberculosis treatment, all patients are still receiving TB treatment, except for one patient who died.

DISCUSSION

In this study, COVID-19 infection rate in TB patients was found as 2.1%. No effect of the coexistence of TB and COVID-19 on morbidity or mortality was observed. Majority of the patients got COVID-19 in the first period of TB treatment. Although the number of patients is small, it can be said that patients with early TB disease and with widespread involvement may be riskier for COVID-19 infection. No drug-drug interactions or drug side effects were observed in our follow-up. Frequent hospital visits by TB patients may be a risk for COVID-19.

In a recent study in which 12.513 COVID-19 patients have been screened, the TB and COVID-19 co-infec-

tion rate has been found to be 1% (6). In a meta-analysis aiming to determine the infection rate of TB in COVID-19 patients, the TB infection rate ranges between 0.37% - 4.47% (7). In this study, TB and COVID-19 co-infection rate was similar to this meta-analysis. Our study population was younger than other studies (6-9). It may depend on this situation that only five patients had comorbidities and were not life-threatening.

COVID-19 involvement was more diffuse in those with extensive involvement at the onset of TB infection. Also, COVID-19 infection was observed more frequently in the first phase of TB infection. Although the number of patients is small, it can be said that patients with early TB disease and with widespread involvement may be riskier for COVID-19 infection.

In four patients, TB and COVID-19 were diagnosed at the same time; this may indicate that clinical and radiological findings may be mixed or they may be together. Although COVID-19 manifests in a broad spectrum from asymptomatic to severe constitutional symptoms and respiratory failure, it usually has an acute onset. Patients can avoid hospital admissions due to relatively subtle and subacute symptoms, as in TB during the pandemic period. Since these cases are admitted to the hospital when they have COVID symptoms, further investigations can be made in cases with suspected TB as in our four cases. Due to the COVID-19 pandemic, it seems inevitable that there will be a delay in TB cases. It may be appropriate for health authorities to determine COVID-free hospitals where examinations and treatments can be performed.

COVID-19 was detected in two patients during hospitalization due to hepatotoxicity related to TB treatment. This may suggest that frequent hospital visits by TB patients may be a risk for COVID-19. In a report by Motta, patients who died due to TB and COVID-19 coexistence got COVID-19 nosocomial. They suggest strict infection control interventions for all hospitalized patients especially those elderly and have comorbidities (5).

In our country, diagnosis and treatment of TB patients are carried out through tuberculosis dispensaries affiliated with the Ministry of Health. During the pandemic period, dispensaries gained importance in terms of reducing the frequent hospital admissions of patients and preventing a delay in diagnosis and treatment. In this study, we think that the diagnosis

and treatment provided by dispensaries have a role in the low COVID-19 infection rate in TB patients compared to the population. TB patients are already more isolated by wearing masks may also play a role in this regard.

Although it has been reported that there may be an interaction between rifampicin and the drugs used in the treatment of COVID-19, no drug-drug interactions or drug side effects were observed in our follow-up (10). Except for one patient who died, all patients completed COVID-19 treatment, and 13 patients are still receiving TB treatment. One patient died due to the progression of pneumonia while receiving COVID-19 treatment. This patient was in the last months of TB treatment and had isoniazid resistance. No conclusion could be obtained that tuberculosis patients suffer more damage or progress more severely than COVID-19 pneumonia. In Karla Therese's study, the data of 12.513 COVID-19 cases have been examined, and they have found 113 (1%) confirmed TB cases. In subgroup analysis, they have found that patients with TB had a 2.17 times higher risk of death than those without (6). However, this study was in the Philippines that have high TB, multi-drug resistance TB, and HIV incidence. As stated in the limitation part of the study, there is no information about HIV infection and TB drug resistance that may affect mortality. In a recent study, it was mentioned that mortality is likely to occur in elderly patients with co-morbidities and drug-resistant strains of *Mycobacterium tuberculosis* can affect mortality (5). The lower mortality rate in our study may be due to the lower average age, the lower number of comorbid diseases and small number of patients.

We have several limitations; firstly, it was a retrospective and single-center study. We got patients followed in a short period, and our study population was small. Also, the absence of multi-drug resistant TB patients in our study leads to incomplete information about the course of these patients.

CONCLUSION

Tuberculosis and COVID-19 diseases are both mortal and important health problems for the whole world. In our study, no effect of the coexistence of TB and COVID-19 on morbidity or mortality was observed. The majority of patients got COVID-19 in the first period of TB treatment. Although the number of patients is small, it can be said that patients with early TB disease and with widespread involvement may be

riskier for COVID-19 infection. Frequent hospital visits by TB patients may be a risk for COVID-19. As in our country, active diagnosis and treatment of TB through dispensaries during pandemic periods will reduce the risk of transmission by reducing the hospital admissions of TB patients.

Ethical Committee Approval: This study approval was obtained from Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Research Ethical Committee (Decision No: 2020/46, Date: 05.11.2020).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: SG, ESAK, EYNÖ

Analysis/Interpretation: SG, EYNÖ, MAU

Data acquisition: SG, ESAK, HÇ

Writing: SG, EYNÖ, MAU

Clinical Revision: SG, EYNÖ, HÇ, MAU

Final Approval: SG, EYNÖ, MAU

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