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Emerging Tuberculosis Among Patients with Previous COVID-19

COVID-19 Geçirmiş Hastalarda Ortaya Çıkan Tüberküloz

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ABSTRACT

COVID-19 patients have a higher incidence of opportunistic infections, but there is little information on tuberculosis (TB). In this study, it was aimed to determine any possible contribution of COVID-19 in TB emergence among patients diagnosed with TB during the pandemic. A retrospective screening of the regional TB laboratory's records identified TB patients diagnosed in the Malatya region between April 1, 2020, and December 31, 2021. Medical data of TB patients with a prior COVID-19 were evaluated. During the study period, 171 TB patients were diagnosed in the region, with 26 also infected with SARS-CoV-2. Patients' histories revealed that 10 (38.5%) of these 26 patients developed TB symptoms in a median 68.5 days after COVID-19. Four patients had one-week to two-month corticosteroid treatment due to severe COVID-19, and one had a hematological malignancy history. However, the remaining five patients had no significant predisposing factor for TB relapse. Four out of 10 patients were free of any finding for active TB before COVID-19. Severe COVID-19 may have some obvious implications for TB reactivation, but there was no conclusive evidence of such an effect in mild to moderate COVID-19. Nonetheless, inquiring about COVID-19 histories from TB patients in large-scale studies may provide high-quality evidence about the interactions between the two pathogens.

Key Words: *COVID-19; SARS-CoV-2 pandemic; Tuberculosis; Tuberculosis reactivation*

ÖZ

COVID-19 Geçirmiş Hastalarda Ortaya Çıkan Tüberküloz

COVID-19 hastaları daha yüksek fırsatçı infeksiyon sıklığına sahiptir ancak tüberküloz (TB) hakkında çok az bilgi vardır. Bu çalışmada, pandemi sırasında TB tanısı alan hastalarda tüberkülozun ortaya çıkışında COVID-19'un olası katkısını belirlemeyi amaçladık. Bölgesel TB laboratuvar kayıtlarının geriye dönük olarak taranması ile Malatya bölgesinde 1 Nisan 2020 ile 31 Aralık 2021 tarihleri arasında tanı konulan TB hastaları saptandı. Tüberküloz tanısı öncesi COVID-19 geçirenlerin tıbbi verileri değerlendirildi. Çalışma süresi boyunca bölgede 171 TB hastası teşhis edildi ve bunların 26'sının SARS-CoV-2 ile infekte olduğu saptandı. Hastaların öyküleri, bu 26

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hastanın 10'unda (%38.5) COVID-19'dan ortalama 68.5 gün sonra TB semptomlarının geliştirdiğini ortaya koydu. Dört hasta şiddetli COVID-19 nedeniyle bir hafta ila iki ay arasında kortikosteroid tedavisi almıştı ve birinin hematolojik kanser öyküsü vardı. Ancak kalan beş hastada TB nüksü için önemli bir predispozan faktör yoktu. On hastanın dördünde COVID-19 öncesi aktif TB bulgusu bulunamadı. Şiddetli COVID-19'un tüberküloz reaktivasyonu için bazı belirgin etkileri olabilir, ancak hafif ile orta dereceli COVID-19'da böyle bir etkiye dair kesin bir kanıt yoktu. Bununla birlikte, büyük ölçekli çalışmalarda TB hastalarının COVID-19 geçmişleri hakkında bilgi sorgulanması iki patojen arasındaki etkileşimler hakkında yüksek kalitede kanıt sağlayabilir.

Anahtar Kelimeler: *COVID-19; SARS-CoV-2 pandemisi; Tüberküloz; Tüberküloz reaktivasyonu*

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a novel pulmonary pathogen that has caused a worldwide pandemic. SARS-CoV-2 infected around 440 million people worldwide by the end of February 2022, resulting in over six million deaths[1]. *Mycobacterium tuberculosis* is one of the oldest pulmonary pathogens of humans and infects around one-third of the global population. It is the leading cause of death from an infectious disease, with 10 million new cases and 1.5 million deaths reported by 2020[2].

A growing body of evidence suggests that SARS-CoV-2 can also trigger a wide range of health problems in humans[3,4]. Low lymphocyte counts are common in patients with coronavirus disease-19 (COVID-19) pneumonia[5], and many of them are treated with corticosteroids to prevent lung damage caused by the dysregulated immune response[6]. These are significant factors that make patients more vulnerable to subsequent infections. Accordingly, Saade et al. have reported an increasing incidence of herpes virus reactivation in patients with severe COVID-19[7]. Additionally, mucormycosis, an opportunistic pathogen of patients with impaired immune performance, was found to be on the rise in patients with active or recovered COVID-19[8]. However, little is known about the interaction of SARS-CoV-2 and *M. tuberculosis*, a bacterium that can survive in tissues for years even in immunocompetent people.

In this study, it was aimed to investigate the potential contribution of COVID-19 to the emergence of TB among patients diagnosed in our region for a period of 21-months.

MATERIALS and METHODS

A retrospective, cross-sectional study was conducted in a city with 800.000 population in the mid-eastern region of Anatolia. Patients diagnosed with TB between April 1, 2020 and December 31, 2021 were identified by screening the data records of the region's TB Diagnostic Laboratory.

The study included TB patients who were diagnosed based on positive TB test results such as Acid-Fast Bacilli (AFB) microscopy, TB culture, and TB-PCR. The Erlich Ziehl Neelsen (EZN) method was used to perform the AFB microscopy. Lowenstein-Jensen medium (RTA Labs., Turkey) and a VersaTREK automated TB culture system were used to perform an eight-week mycobacterial culture (TREK Diagnostic Systems, USA). The DNA of *M. tuberculosis* complex strains was detected in the samples using GeneXpert MTB/RIF Ultra assay kits (Cepheid Inc., USA).

TB patients who also had COVID-19 were determined by searching the Turkish Health Ministry's Laboratory Information and Management System (LBYS), a web-based national database that is updated with daily SARS-CoV-2 PCR test results.

Demographic and medical information for the patients was gathered from the records of the region's TB Diagnostic Laboratory and the central TB dispensary which was in charge of registering patients for anti-TB treatment. Patients' data on the onset of TB symptoms was obtained from their medical histories and compared to the dates of their COVID-19 diagnosis.

This study was approved by İnönü University Health Sciences Ethics Studies Council (3074/2022).

Table 1. Characteristics of 10 TB patients who had TB symptoms after their COVID-19 courses

Patient	Age	Sex	[a]Days to TB after COVID-19	AFB Grade	TB History	Severity of COVID	Co-Morbidity	TB Involvement
A	16	M	77	-	-	Moderate	None	Axillary lymph node
B	43	M	106	-	-	Mild	None	Pulmonary
C	59	M	45	-	-	Moderate	CMML*, cancer chemotherapy	Axillary lymph node
D	71	F	90	-	-	Moderate	Diabetes mellitus, dexamethasone treatment for 1-week	Intestinal
E	65	F	60	-	-	Moderate	COPD**	Pulmonary
F	31	M	15	1+	+[b]	Mild	None	Cervical lymph node
G	65	F	55	3+	+[c]	Severe	Severe COVID-19, lymphopenia, prednisolone treatment for 2-months	Pulmonary
H	74	F	160	1+	-	Moderate	Prednisolone treatment for 1-week	Pulmonary
I	61	M	90	4+	-	Severe	Severe COVID-19, lymphopenia, prednisolone treatment for 3-week	Pulmonary
J	19	F	40	4+	-	Mild	None	Pulmonary

[a]The time interval from COVID-19 diagnosis to the emergence of TB symptoms; [b]TB-lymphadenitis, determined two years ago; [c]Pulmonary TB, during childhood.
*CMML: Chronic myelo-monocytic leukemia; **COPD: Chronic obstructive pulmonary disease.

RESULTS

A total of 171 patients were diagnosed with TB in the province during the study period. Median age of the patients was 54.5 years (min= 4, max= 92), 94 (%55) were males and 110 (64.3%) were pulmonary TB.

A total of 26 TB patients had COVID-19 until the end of the study. The patients' data about TB symptom emergence indicated that 10 (38.5%) out of 26 patients developed TB symptoms in a median of 68.5 days (min-max= 15-160 days) after COVID-19.

The medical records of these 10 patients were analyzed for the potential risk factors that could lead to TB reactivation. Due to severe COVID-19, four patients (three with pulmonary TB and one with intestinal TB) received corticosteroid treatment for one week to two months, while the other six received no immune-regulatory medication. A 59-year-old patient with chronic myelomonocytic leukemia who developed TB lymphadenitis 45 days after mild COVID-19 was ignored. The remaining five patients had no significant medical issues that could be attributed to TB reactivation.

Four patients were found to be free of any finding indicating active TB during or before their COVID-19 diagnoses, but there was no data for the remaining six patients. The characteristics of the ten patients are shown in the Table 1.

DISCUSSION

Several effector cells and complex mechanisms are involved in the immune response to *M.*

tuberculosis. The bacilli are confined by macrophages in the Ghon complex which is surrounded by T-helper, cytotoxic, and regulatory T-cells, B-lymphocytes, natural killers, and dendritic cells[9]. Problems with these immunocytes or response pathways result in multiplication and leaking of the bacilli, as well as disease reactivation, which explains the increased TB relapse in people infected with HIV or taking immune-suppressive medications.

Studies have shown that severe COVID-19 could be associated with a substantial reduction in lymphocytes subsets, and the COVID-19-mediated dysfunctions in the effector cells did not improve completely even after six months of the infection[10]. Furthermore, when infected with SARS-CoV-2, macrophages, one of the virus's main targets, fail to clear dead or dying cells, which is required for proper tissue injury resolution[11]. Moreover, a recent study has shown that coronavirus infection resulted in intracellular multiplication of the TB bacilli and extracellular release by activating an altruistic defense mechanism in mesenchymal stem cells in the latently-infected mice with TB[12]. The authors have also stated that the potential role of COVID-19 in TB reactivation in humans should be determined to avoid a future TB pandemic.

TB relapses have been reported in patients with severe COVID-19 and a history of using corticosteroids and/or immune regulatory drugs (e.g., tocilizumab), as well as low lymphocyte counts due to SARS-CoV-2 infection[13,14]. This study showed that four patients had moderate to severe COVID-19 and corticosteroid use between 55 and 160 days before their TB symptoms appeared (Table 1). One of these patients could be proven to be free of any medical finding for active TB before or during the COVID-19 diagnosis.

Data on SARS-CoV-2's ability to revive TB even in milder infections is severely limited. In a cohort study, Tadolini et al.[15] have reported that 14 (28.5%) patients who were mostly immigrants and young individuals developed active TB following COVID-19. The authors have speculated that COVID-19 could have triggered TB reactivation because 11 of the 14 patients were from TB-endemic countries, and they concluded that more research was needed to better understand the interaction between these two pathogens. Khayat et al. have reported a case of TB recurrence in a 40-year-old female emerged seven weeks after a mild COVID-19 course. The authors have concluded that the patient's TB reactivation was most likely due to CD4+ T-cell depletion caused by the SARS-CoV-2 infection[16]. In another study, Alkan et al. have reported a 66-year-old female who was diagnosed with TB realpse after recovering from mild COVID-19[17].

We carried out this study in a regional setting in Türkiye, a country with a TB incidence of 13.5 cases per 100.000 people, and approximately 9% of annual cases were relapses[18]. We screened patients with TB who also had COVID-19 and found that nearly 40% of these patients' TB symptoms appeared in the weeks or months following COVID-19, which were initially thought to be subsequent health problems related to COVID-19. Though our total 152 TB patients had 14 different TB involvements, six of these 10 patients had pulmonary TB, three had lymphadenitis, and one had intestinal TB. Such involvement areas were also the particular tissues where SARS-CoV-2 replicated and interacted with the immunocytes effectively[3].

We were able to show that a total of four TB patients did not have active TB before or during their COVID-19 diagnosis, but there was no medical record for the remaining six patients. This is one of the study's major limitations. We could have determined whether mild to moderate COVID-19 had any significant effect on TB reactivation if we could have proven that none of our patients had active TB at the time of or shortly before their COVID-19 courses.

The study's results suggested that severe COVID-19 could cause TB relapse. Given the high global prevalence of both infections, such an interaction could have a significant negative impact on national TB control programs. Our findings, on the other hand, do not directly imply that a previous mild COVID-19 infection can lead to TB reactivation. Comprehensive studies on a national or international scale are

required to gain a better understanding of the potential interaction. Querying COVID-19 histories in TB patients will aid in better identifying the problem, and TB should be considered when new lung symptoms appear in people who have previously had a COVID-19.

CONFLICT of INTEREST

None of the authors had conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: All of authors

Analysis/Interpretation: All of authors

Data Collection or Processing: YY, EST, HE

Writing: YY, BO

Review and Correction: YY, EST, BO

Final Approval: All of authors

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