

Coronavirus Pandemic

Tuberculosis and COVID-19: An overlapping situation during pandemic

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Abstract

Introduction: The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease 2019 (COVID-19). First COVID-19 case was detected in March, 10, 2020 in Turkey and as of May, 18, 2020 148,067 cases have been identified and 4096 citizens have died. Tuberculosis (TB) is a worldwide public health concern, incidence of tuberculosis (per 100,000 people) in Turkey was reported at 14, 1 in 2018. During pandemic COVID-19 was the main concern in every clinic and as we discuss here overlapping respiratory diseases may result in delaying of the diagnosis and treatment.

Methodology: There were 4605 respiratory samples examined between March 23 and May 18 for COVID-19 and 185 samples for *Mycobacterium tuberculosis* in our laboratory. The Xpert Ultra assay was performed for the diagnosis of pulmonary tuberculosis; SARS-CoV-2 RNA was determined by real-time PCR (RT-PCR) analysis in combined nasopharyngeal and deep oropharyngeal swabs of suspected cases of COVID-19.

Results: Both of SARS-CoV-2 and *M. tuberculosis* tests were requested on the clinical and radiological grounds in 30 patients. Here we discussed 2 patients who were both COVID-19 and TB positive. One patient already diagnosed with tuberculosis become COVID-19 positive during hospitalization and another patient suspected and treated for COVID-19 received the final diagnosis of pulmonary TB and Human Immunodeficiency Virus infection.

Conclusions: We want to emphasize that while considering COVID-19 primarily during these pandemic days, we should not forget one of the “great imitators”, tuberculosis within differential diagnoses.

Key words: COVID-19; *Mycobacterium tuberculosis*; SARS-CoV-2; PCR.

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Introduction

March 24 was the World Tuberculosis Day, but this year tuberculosis was overshadowed by the COVID-19 pandemic [1]. Since the World Health Organization (WHO) declared the outbreak of novel coronavirus (COVID-19) as a Public Health Emergency of International concern on Jan 30, 2020, COVID-19 affected 3,917,366 cases and 274,361 deaths were recorded by May 18 [2]. The first case detected on March 10 in Turkey and according to the data of the Turkish Ministry of Health, 148,067 cases have been identified and 4096 citizens have died by May 18. Incidence of tuberculosis in Turkey was reported as 14,

1 cases per 100,000 population with 0.70 mortality rate [3-4].

The immune status that makes people vulnerable to tuberculosis may also make them susceptible to coronavirus infection. COVID-19 is already affecting control measures for tuberculosis whereas possibility of coinfection should be kept in mind. Culture and antimicrobial susceptibility testing are still considered as gold standard for diagnosis of tuberculosis, however due to lack of access to mycobacteriology laboratory facilities in many center, point of care tests are required for early diagnosis and to prevent dissemination of drug resistance strains all over the world. Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) is the most

commonly used point-of-care assay for tuberculosis (TB) that was endorsed by WHO in December, 2010. Since the end of March 2017, WHO has recommended the replacement of Xpert by Ultra (Ultra, Cepheid, Sunnyvale, California) as an advanced version with better TB detection capabilities and more definitive identification of rifampicin resistance [5]. We have replaced Xpert MTB/RIF assay with Ultra assay in 2019 in our hospital, which is localized in Istanbul, Turkey with 17 million inhabitants.

Since the end of March, when the first COVID-19 case was diagnosed in Turkey, we have mainly focused for diagnosis of COVID-19 cases in our laboratory and molecular tests were preferred for diagnosis due to their rapidity. We slowed down other activities in the laboratory and shifted our staff for COVID-19 diagnosis. Here, we analyzed two cases with confusing clinical and laboratory tests who are admitted to our hospital during pandemic and reviewed literature to guide clinicians for differential diagnosis of patients with respiratory symptoms.

Methodology

Between March 23 and May 18, 4605 respiratory samples for COVID-19 and 185 samples for *Mycobacterium tuberculosis* were sent to microbiology laboratory. Both of SARS-CoV-2 and *M. tuberculosis* tests were requested on the clinical and radiological grounds in 30 patients. The study protocol was approved by the Institutional Review Board and the Ethics Committee of Marmara University Faculty of Medicine (09.2020.676).

Diagnosis of COVID-19 infection: According to the Turkish Ministry of Health diagnostic guideline, SARS-CoV-2 RNA is investigated by RT-PCR method in the combined nasopharyngeal and oropharyngeal swab (cONS) samples of suspected cases [6].

Respiratory samples were collected from patients with acute respiratory illness (fever and at least one signs/symptoms of respiratory disease, e.g., cough, shortness of breath) with either a history of travel to a location reporting community transmission of COVID-19 disease or having been in close contact with a confirmed COVID-19 case in the last 14 days prior to symptom onset; or a patient with severe acute respiratory illness requiring hospitalization without an alternative diagnosis that fully explains the clinical presentation.

Viral RNA was extracted by using Bio-speedy® viral nucleic acid buffer (Bioexen LTD, Istanbul, Turkey) and RT-PCR was performed with Bio-speedy® COVID-19 qPCR detection kit, Version 2

(Bioexen LTD, Istanbul, Turkey) using primers and probes targeting the RNA-dependent RNA polymerase (RdRp) gene fragment in a LightCycler® 96 System (Roche, Basel, Switzerland). Each 20 µL reaction mixture contained 5 µL of Oligo Mix, 10 µL of 2X Prime Script Mix and 5 µL of RNA as the template. The thermal cycling condition was 15 minutes at 45°C for reverse transcription, 3 minutes at 95°C for PCR initial activation, and 45 cycles of 5 seconds at 95°C and 35 seconds at 55°C according to the manufacturer's instructions (Bioexen LTD, Istanbul, Turkey). Oligo Mix contains internal control (IC) targeting Human RNase P gene as an extraction control. A positive and a negative control were included in each run to generate a valid result. A Ct value of less than 40 was defined as the positive result. Analytical and clinical performance of the kit was determined by the "Turkish Ministry of Health, General Directorate of Public Health, Department of Microbiology Reference Laboratories and Biological Products (HSGM)". The analytical sensitivity of the kit is 99.4% and its specificity is 99.0%.

Diagnosis of *Mycobacterium tuberculosis*: Xpert Ultra assay was done by adding sample reagent to the first collected sputum specimen in a 2:1 dilution, and 2 mL of the resulting mixture was added to Xpert Ultra cartridge (Cepheid, Sunnyvale, CA, USA). Smear microscopy was done using Ziehl-Neelsen and auramine-rhodamine staining. 0.5 mL of the resuspended pellet was inoculated into liquid culture using mycobacteria growth indicator tube (MGIT) with a BACTEC 960 instrument (BD Microbiology Systems, Sparks, MD, USA), and 0.2 mL was inoculated on Löwenstein-Jensen medium. Cultures positive for growth of acid-fast bacilli underwent confirmation of *M. tuberculosis* complex by MPT64/MPB64 antigen detection.

Both of SARS-CoV-2 and *M. tuberculosis* tests were requested on the clinical and radiological grounds in 30 patients. Characteristics of the patients were given in Table 1.

Here, we discussed 2 patients who were both COVID-19 and TB positive.

Patient 1: UA, 77 years of age, female

She was admitted to the hospital on April 3, 2020 with the complaints of non-productive cough and respiratory difficulty. On physical examination, she was afebrile and laboratory analysis revealed that oxygen saturation with pulse oximeter was (SaO₂) 87% in room air, CRP: 8 mg/L, LDH: 145 U/L. She had underlying diabetes mellitus, hypertension, chronic obstructive

lung disease, and she was also a hemodialysis patient related with chronic kidney failure and on thrice-weekly hemodialysis. Previously, she has been admitted to intensive care unit twice due to respiratory failure.

CT scan showed loss of volume in right upper lobe which was present on a previous scan 6 weeks ago. The finding is suspected for endobronchial lesion and showed no change during this time. There was also tree-in-bud pattern in the right lobe suggesting non-specific infection which was a new finding. Pleural and pericardial effusions and volume overload were also noted.

There was no history of contact with a positive person and SARS-CoV-2 PCR was negative. Treatment was planned for congestive heart failure and lung edema. Piperacillin- tazobactam 4×2.25 mg IV has been given for 10 days.

Bronchoscopy was performed in April 15, 2020 and bronchial lavage sample was sent to microbiology laboratory. Bacterial culture revealed no specific bacteria, unfortunately tuberculosis culture was not available at that time. Since Xpert Ultra assay was positive for *M. tuberculosis*, anti-TB therapy was planned.

Two weeks later, she had high fever (38.2 °C), respiratory difficulty and tachypnea with increased CRP (155 mg/L) and LDH (303 U/L) levels. CT scan showed progression of tree-in-bud pattern and this time there were multiple ground-glass lesions with predominantly sub pleural distribution strongly suggesting COVID-19 infection. SARS- CoV-2 PCR result was found to be positive from nasopharyngeal sample. She was treated for COVID-19 with favipiravir 200 mg 2×3 po (loading dose 2×1600 mg, maintenance dose 2×600 mg po for a total of 5 days), hydroxychloroquine 200 mg 2×1 po (loading dose of 2×400 mg, maintenance dose 2×200 mg po) for 5 days and after completing COVID-19 specific treatment, anti- TB treatment has started.

Patient 2: SM, 39 years of age, female

She was admitted to the hospital with coughing and sputum production for 1 week, in April 21, 2020. She had diarrhea 15 day previously. On admission, low WBC count (3700/ µL) and remarkable lymphopenia was recorded. CT scan showed multiple mediastinal lymphadenopathies (LAP) some calcified right upper lobe pneumonia, and bilateral nodular lesions accompanied by ground-glass opacities. The findings were consistent with infection although not specific for COVID-19. SARS- CoV-2 PCR was negative from

Table 1. Characteristics of the patients whom both of SARS-CoV-2 and *M. tuberculosis* tests were requested (n=30).

Characteristics	n	%
Gender		
Male	21	70.00
Female	9	30.00
Age, years	Median	IQR
Male	38	3-86
Female	39	9-86
Chronic Comorbidities	n	%
Hypertension	5	16.70
Chronic heart disease	6	20.00
Chronic lung disease	9	30.00
Diabetes Mellitus	5	16.66
*Immunosuppression	8	26.66
None	7	23.33
Severe Disease	n	%
ICU admission	12	40.00
Exitus	3	10.00

*Malignancy, hematopoietic stem cell transplantation, HIV positive status.

nasopharyngeal sample. Increased levels of LDH (349 U/L) and CRP (17.6 mg/L) was detected. Treatment for COVID-19 was started with azithromycin 1×250 mg po (loading dose of 1×500 mg followed by a maintenance dose of 1×250 mg po for a total of 5 days) and plaquanil 200 mg 2×1 po.

One week later, sputum production was increased with high fever of 38.4 °C and repeated specimens were sent for COVID-19 diagnosis. Bacterial culture revealed no significant pathogen. SARS- CoV-2 PCR was negative from swab samples and also from sputum sample. Repeat CT showed progression of parenchymal nodularity and especially ground-glass opacities. Tazocillin 4×4.5 mg po, ciprofloxacin 2×400 mg po were added. Since symptoms persisted despite treatment, sputum was sent for *M. tuberculosis* and Xpert Ultra assay was found to be positive. Direct examination of smear with EZN revealed acid fast bacilli and anti-tuberculosis treatment was started. Mycobacterium culture became positive after 15 days of incubation. As tuberculosis is one of the clinical indicator conditions for HIV testing, HIV 1-2 Ab+Ag EIA test was requested and found positive. HIV-1 RNA viral load was 12,957 copies/mL.

Discussion

The COVID-19 epidemic offers the opportunity to make some assessments on the sharing aspects between COVID-19 and TB as well as the challenges and lessons learned from the control efforts of each of them that could be of mutual benefit. Timely and rapid diagnosis and public awareness are the mainstay for control of both diseases.

Policies widely adopted in response to the ongoing pandemic of Covid-19, particularly reassignments of health personnel and equipment, are impacting the performance of TB prevention and care programs. A recent review stated that global TB case detection decrease by an average 25% over a period of 3 months (as compared to the level of detection before the pandemic), will lead to a predicted additional 190,000 (56,000 – 406,000) TB deaths (a 13% increase), bringing the total to 1.66 (1.3 – 2.1) million TB deaths in 2020, near the global level of TB mortality of the year 2015 [7].

There is limited data about the coinfection with tuberculosis and COVID-19. He *et al* [8] reported 3 tuberculosis cases with COVID-19 infection. Although viral diagnosis was done by a real-time fluorescence polymerase chain reaction assay, the hospital restricted the laboratory tests for diagnosis of tuberculosis. Coinfection was determined by patient's history, biochemical tests and chest X-ray. All the patients received antiviral therapy including lopinavir/ritonavir, and arbidol. All of the patients recovered and were discharged from the hospital. However, on the 9th day after discharge, patient 2 had a recurrence of SARS-CoV-2 RNA positivity and returned to the hospital to remain in isolation and under observation. These case reports remind us of the possibility of TB coinfection in COVID-19 patients with incomplete recovery, as well as the importance of careful use of steroids for their case management.

Bronchoscopic sampling was performed in the first hospitalization of our first case, because a non-COVID19 pathogen was considered and patient was discharged due to pandemic. But the patient's failure to receive the result on time delayed the treatment plan for 15 days and unfortunately the patient was also infected by SARS-CoV-2 which makes the treatment choices even more complicated due to drug interactions.

It is also possible that in patients with cough, fever and difficulty breathing due to similarity in symptoms of tuberculosis and COVID-19, COVID19 therapy may be started more frequently than usual during the pandemic period. Radiology is very critical for diagnosis especially in PCR negative patients however in our second case it was not possible to exclude COVID-19 by radiology and treatment was started. Since there was no clinical improvement, sputum examinations were repeated and tuberculosis was eventually diagnosed 3 weeks after the initial symptoms.

COVID-19 pandemic offers the opportunity to make some assessments on the sharing aspects between

COVID-19 and TB as well as the challenges and lessons learned from the control efforts of each of them that could be of mutual benefit [1, 9]. Importance of timely and rapid diagnosis is important since isolation of the infected patient is the most important preventive measure. Considering the nosocomial transmission possibility of TB among COVID-19 infected patients, rapid molecular methods like Xpert Ultra must be the choice for avoiding diagnostic delay.

The response to the COVID-19 pandemic may bring opportunities for synergies including increased levels of TB testing, particularly in high-HIV settings where symptoms of TB and COVID-19 disease are more difficult to differentiate clinically, better implementation of infection control measures and more effective contact tracing investigations [10]. As the COVID-19 pandemic sweeps into countries like South Africa where the decades were spent in fighting the world's worst combined epidemic of tuberculosis (TB) and HIV, pandemic's impact could worsen the situation and diagnostic facilities should be immediately expanded by policy makers [11].

Conclusions

In the future, SARS-CoV-2 might subside as was the case of SARS in 2003 or humanity will have to coexist with it until a vaccine becomes available. However, TB remains a long-standing public health problem and is still the no 1 killer among the infectious causes of death.

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