Severe Acute Respiratory Syndrome Coronavirus-2 and Pulmonary Tuberculosis Coinfection: Double Trouble

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Case Report

Keywords: COVID-19, SARS-CoV-2, Tuberculosis, Coinfection, Case report

Posted Date: August 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-22464/v4

Version of Record: A version of this preprint was published on August 18th, 2020. See the published version at https://doi.org/10.4103/INJMS.INJMS_72_20.

Abstract

Background: The ongoing pandemic of novel coronavirus disease 2019 (COVID-19) has received worldwide attention by becoming a major global health threat. We encountered one case with COVID-19 and tuberculosis (TB) coinfection which has not been frequently reported.

Case presentation: A 76 year old female presented with acute respiratory symptoms superimposed on chronic symptoms, suggestive to have pneumonia. Oropharyngeal throat swab sample for COVID-19 was positive as detected by real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay. GeneXpert Ultra detected Mycobacterium tuberculosis complex with Rifampicin resistance indeterminate. Patient was treated with appropriate management.

Conclusion: Clinicians should suspect coinfection with TB during ongoing pandemic of COVID-19 as therapeutic strategies need to be determined timely to improve outcome and prevent transmission in community.

Background

The 2019 novel coronavirus (2019-nCoV) or recently renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by World Health Organization (WHO), has been rapidly spreading with emergence from Wuhan City of Hubei Province of China in December 2019 to the rest of the world involving 203 other countries. [1, 2] Disease associated with SARS-CoV-2 also termed as Coronavirus disease 2019 (COVID-19), has now become a major threat to global health. WHO has declared this disease as a pandemic on 11th March 2020. Since then (as on 20th June, 2020), almost 8.5 million confirmed cases with 0.45 million deaths have been reported worldwide. [2] The clinical features of COVID-19 are variable, ranging from asymptomatic state to pneumonia, acute respiratory distress syndrome and multi-organ dysfunction. Tuberculosis (TB) is already existing as unprecedented pandemic worldwide with estimated 10 million with mortality of 1.2 million among HIV-negative, and an additional 0.25 million among HIV positive people mortality of 1.2 million in 2018. [3] Around one-fourth of world population estimated to have latent TB infection (LTBI). [3] Convergence of TB and COVID-19 pandemics will be more deadly with propensity to cause sustained community transmission across all countries. To our knowledge, the coinfection of SARS-CoV-2 and TB has been reported with limited evidence. Here, we present one case of coinfection of SARS-CoV-2 and TB.

Case Report

A 76 years old female presented to our emergency on 20th March, 2020 with a 1.5 month history of low grade intermittent fever, non-productive cough and decreased appetite with an eventual weight loss of 4 kg. She had worsening of symptoms five days prior to presentation with high grade fever followed by breathlessness 3 days prior to her presentation. There was no prior history of pulmonary TB, any recent hospital admission and no known contact with patients or family members having active TB. Her

background history revealed that she was hypertensive taking tablet amlodipine 10 mg once daily. On physical examination at the time of admission, the patient was febrile (102°F) and had an arterial blood pressure of 140/80 mmHg, a heart rate of 110 beats/min, respiratory rate of 32 breaths/min and oxygen saturation of 86% on room air. Chest auscultation revealed bilateral crepitation with bronchial breathing on left side. Findings of the remainder of the systemic examination were unremarkable. The arterial blood gas on room air showed a PaO2 of 52 mmHg (Normal range: 80-100), PaCO2 of 30 mmHg (Normal range: 35-45), HCO3 of 18 mmol (Normal range: 22-26), pH of 7.46 (Normal range: 7.35-7.45) and wide alveolar-arterial gradient of 36 mm Hg (Expected normal value- 23) suggestive of acute hypoxemic respiratory failure. Routine blood tests revealed the following: hemoglobin level of 11.5 g/dL (Normal range: 12-15 g/dl), leucocyte count of 7600 cells/mm^3 (Normal range: 4000-11000 cells/mm^3) with 90% neutrophils (Normal range: 40%-80%), 7.0% lymphocytes (Normal range: 20%-40%), and 3.0% monocytes (Normal range: 2%-10%), platelet count 220,000/mm^3 (Normal range: 150,000/mm^3-410,000/mm^3), serum sodium level 133 mmol/L (Normal range: 135-145 mmol/l), urea 62.7 mg/dL (Normal range: 16-48 mg/dl) and creatinine 2.72 mg/dL (Normal range: 0.7-1.2 mg/dl). The erythrocyte sedimentation rate was elevated with 65 mm (Normal range: 0-30 in 1^{st} hour). Other remarkable blood test findings included serum lactate dehydrogenase 550 U/L (Normal range: 135-225 U/L), High sensitive C-reactive protein- 55 mg/l (Normal value: < 5 mg/l), procalcitonin 0.5 ng/ml (Normal range: 0.0-0.5 ng/ml), NT-pro Brain Natriuretic Peptide level 600 pg/ml (Normal range: 0-249 pg/ml), ferritin level 426.2 ng/ml (Normal range: 13-150 ng/ml), troponin-I negative, creatine phosphokinase (CPK) 430 U/L (Normal range: 0-200 U/L) and CPK-MB 30.7 U/L (Normal range: 0-25 U/L). Chest radiograph revealed left lower zone alveolar opacity likely lobar consolidation as shown in **Figure 1A.** Computed tomography (CT) thorax revealed left lower lobe dense consolidation having air bronchogram with underlying effusion and bilateral ground glassing as shown in **Figure 1 (B-F).** Provisional diagnosis of community acquired pneumonia was established initially. A therapeutic trial of intravenous antibiotics (Ceftriaxone 1gm twice daily and Azithromycin 500 mg once daily) was initiated after collection of cultures along with other supportive measures. Ziehl Neelsen staining of two consecutive sputum smear samples were negative for acid fast bacilli (AFB). Her oxygenation was maintained with SpO2 around 95% with simple face mask with flow rate 8 litre/minute on admission. A short trial of intermittent non-invasive ventilation was also provided to reduce work of breathing even after achieving oxygenation. Aerobic culture of sputum, blood and urine collected at admission, were sterile. A 2D echocardiogram revealed mild concentric left ventricular hypertrophy with preserved ejection fraction, grade 1 diastolic dysfunction and no vegetations. Throat swab was negative for respiratory viruses including influenza. Serology was negative for HIV, hepatitis B and C. In view of the height of novel SARS CoV-2 pandemic worldwide, throat swab for SARS CoV-2 was also sent and found to be positive as detected by validated real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for both E-Sarbeco and RdRP genes. GeneXpert Ultra of sputum revealed rifampicin indeterminate *Mycobacterium tuberculosis* complex (MTBC). It was advised in view of high clinical suspicion for TB with chronicity of symptoms and radiological findings. Based on these reports, history of patient was again reviewed after enquiring all family members staying along with her. She was confirmed to have had direct contact with her grandson who travelled from France 12 days prior to the onset of acute symptoms and returned back after five days. Thereafter, her grandson also turned out to

be COVID-19 positive. The treatment was modified on lines of COVID-19 that included injectable azithromycin 500 mg IV once daily, injectable methylprednisolone 40 mg IV twice daily, tablet hydroxychloroquine 400 mg twice daily for first day followed by 400 mg once daily for 4 days, tablet vitamin C 500 mg twice daily and tablet N-acetyl cysteine 600 mg twice daily. Anti-tuberculous regimen (Rifampicin-R, Isoniazid-Z, Ethambutol-E and Pyrazinamide-Z) was also started for TB component. No adverse events were reported. Patient was shifted to COVID-19 designated hospital on 24th March 2020 for further management as per national policy guidelines. Written informed consent was obtained from the patient for using clinical records in this study.

Discussion

We have reported this case with particular interest due to coinfection of SARS-CoV-2 and pulmonary TB which is less frequently reported. There are studies that have reported coinfection of SARS-CoV-2 with other respiratory pathogens particularly influenza virus. [4-7] Few studies have previously reported coinfection of TB with other coronaviruses SARS-CoV-1 and MERS-COV during outbreaks in 2003 and 2012 respectively. [8-11] Most of cases were having pulmonary TB initially followed by viral superinfection [8, 9, 11] while few contracted TB after recovery from viral infection. [10] Co-infection of TB and COVID-19 can also exist as there is the possibility that both could augment each other with transient decrease in cellular immunity leading to new infection or exaggerated reactivation of latent infection, based on previous experience with other coronaviruses. This relationship could not be underestimated as few studies have recently reported coinfection of SARS-CoV-2 with TB as summarized in **Table 1**. [12-19] An observational study recently reported that persons with latent TB have increased susceptibility for SARS-CoV-2 infection associated with rapid progression and severe involvement. [16] TB infection was more common among patients with SARS-CoV-2 infection than in those with bacterial or other viral infections. A retrospective multicentric study belonging to Global Tuberculosis Network (GTN), reported that COVID-19 can occur before, simultaneously, or after the diagnosis of TB. [17] Although this coinfection might be a mere coincidence but there could be a temporal relationship. [12, 13] This could be due to insufficient infection control practices compounded by a higher susceptibility of TB cases. [13] SARS-CoV-2 can induce type 1 interferons that inhibit immune responses mediated by interferon-gamma leading to flare up of TB infection, as observed for infections with other viruses like influenza and SARS-CoV-1. [20] However, a recent study observed that SARS-CoV-2 did not significantly induce any types of interferons and only upregulated few pro-inflammatory cytokines or chemokines unlike SARS-CoV-1. [21] More evidence is required regarding this coinfection. Differentiation between TB and SARS-CoV-2 is quite difficult as both can manifest with similar respiratory symptoms like fever, cough, breathlessness and weakness but there is gradual or chronic progression of symptoms in TB as compared to acute or rapid progression in case of COVID-19. Both also share common risk factors like advanced age, diabetes, malnutrition, immunosuppression and other chronic illnesses. The radiological picture of unilateral non-cavitating consolidation with effusion and bilateral ground-glassing on CT thorax is atypical for both pulmonary TB as well COVID-19. [22, 23] To be able to assign it to either of the two pathologies definitely is seemingly challenging as reported in other studies. [12, 13, 17] Radiologists are still trying to explore

definite radiological patterns for novel COVID-19. A study from Italy reported no characteristic radiological features for COVID-19 in most of the cases with coinfection. [13] Our patient tested positive for both RT-PCR and GeneXpert Ultra for COVID-19 and MTBC respectively. We advised GeneXpert despite smear negative for AFB as per policy framed by National TB Elimination Programme (NTEP) of India. [24] There is possibility that these results could be false positive. It is recommended that genotypic tests should be repeated or confirmed with gold standard culture and phenotypic drug susceptibility test for M. tuberculosis to reconfirm findings. Both these tests are highly specific for diagnosing respective diseases and unlikely to be false positive. The results of conventional culture are usually delayed by three to six weeks whereas liquid culture are prone to contamination. A study reported that diagnosis of TB was confirmed by culture in 14 out of 18 COVID-19 patients as detected by GeneXpert MTB/RIF. [13] It becomes quite uncertain whether to continue treatment or not for remaining 4 patients as diagnosis of TB becomes questionable. Appropriate clinical judgement is warranted in order to avoid unfavourable outcomes in such patients. Timely initiation of treatment should be our priority in these subset of patients especially in high TB burden settings. Genotypic tests should be advised for rapid diagnosis of these patients to achieve early initiation of treatment and curbing nosocomial as well as community transmission in this ongoing pandemic. Since our patient was having history of contact, advanced age, hypertension and acute kidney injury, the presence of this co-infection was suspected and management for both infection was initiated. Treatment was initiated early due to severity of illness that was predicted on the basis of strong clinical suspicion and laboratory findings. Neutrophil-lymphocyte ratio was also high (12.85) in our case that suggest poor prognosis. This is in accordance with an observational study from China that proposed neutrophil-lymphocyte ratio as one of the parameter for severe disease. [25] It also further highlights the point that no single radiological pattern can safely rule in or rule out either COVID-19 in a pandemic situation or TB in a high burden country like India. TB with Human Immunodeficiency Virus (HIV) co-infection is also prevailing in many countries. The situation will be more difficult to tackle if there is associated drug resistance. Patients of COVID-19 either having active TB infection or previous history of TB with or without sequelae, will be more at risk of worse outcomes. However, larger studies are required to unveil this association for further validation. It can be anticipated that as more number of cases are evolving, we might encounter the most deadly combination of drug-resistant TB (DR-TB), HIV and COVID-19. The limitation of our study is lack of data regarding treatment response and outcome. Unfortunately, culture sample of our case got contaminated and could not be repeated as patient was referred to COVID-19 designated hospital according to prevailing national policy. Few studies have supported the fact that these patients require serial monitoring with clinical, radiological and microbiological assessment not only to confirm diagnosis but also to track treatment response, any adverse events or drug interactions and outcome. [13-15] Our purpose of reporting this case was just to highlight the possibility of coexisting infections in high burden countries for TB like India which are also facing COVID-19 pandemic. Therapeutic strategies like intense monitoring, timely decision for implementing appropriate ventilatory strategies, aggressive contact tracing, appropriate infection control and use of steroids or other immunosuppressive drugs like IL-6 inhibitor (Tocilizumab) for COVID-19, need to be prioritized with these subset of patients to avoid severity or complications. [26, 27]

Conclusions

Clinicians should remain cautious while dealing cases of COVID-19 and TB coinfection particularly in countries where TB is endemic. Suspicion of TB (a chronic disease) in cases of COVID-19 (acute illness) should be made if there is a long antecedent history as in this case, or if the patient fails to improve in atleast two weeks' time. Diagnosis of TB must not be missed or delayed in view of ongoing COVID-19 pandemic as it may lead to poor outcome and enhanced transmission of infection in community if left untreated.

Abbreviations

2019-nCoV: 2019-novel coronavirus

AFB: Acid Fast Bacilli

BCG: Bacillus Calmette-Guerin

COVID-19: Coronavirus disease 2019

CPK: Creatine Phosphokinase

CT: Computed tomography

DR-TB: Drug Resistant Tuberculosis

HIV: Human Immunodeficiency Virus

IGRA: Interferon Gamma Release Assay

LTBI: Latent Tuberculosis Infection

MERS-CoV: Middle East Respiratory Syndrome Coronavirus

MTBC: Mycobacterium tuberculosis complex

RT-PCR: Reverse Transcriptase–Polymerase Chain Reaction

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2

TB: Tuberculosis

WHO: World Health Organization

Declarations

Ethics approval and consent to participate: The ethical committee of Ayushman Hospital and Health Care, Dwarka, Delhi approved the study. Consent taken from patient. We also certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

Consent for publication: The authors certify that they have obtained all appropriate patient consent forms.

Availability of data and material: The patient has given consent for images and other clinical information to be reported in the journal. The patient understands that their names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Competing interest: Nil

Funding: Nil

Authors' contributions: AS, AG and KD made substantial contributions to the conception or design of the work; **AS, AG and KD** interpreted data; **AS, AG and KD** have drafted the work or substantively revised it; **AS, AG and KD** have read and approved the manuscript; **AS, AG and KD** declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the CARE Network. All authors have read and approved the manuscript and ensured that this is the case.

Acknowledgements: Nil

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Tables

Table 1:- Characteristic of studies reporting TB and COVID-19 coinfection

	Number of cases reported with TB and COVID-19 coinfection	Findings of study
i	49 Male-40 (81.6%) Female-9 (18.4%)	Active TB-42 (85.7%); Post TB sequelae-7 (14.3%) Pulmonary TB-48 (97.9%) Extra-pulmonary TB-13 (26.5%) Drug resistant TB-8 (16.3%) BCG vaccination- 19/30 (63.3%) HIV infection-6/48 (12.5%) Confirmed SARS-CoV-2 infection- 46 (93.9%) Diagnosis by HRCT thorax-3 (6.1%) TB before COVID-19 diagnosis-26 (53.0%) TB after COVID-19 diagnosis-14 (28.5%) Diagnosis of TB and COVID-19 simultaneously or within 7 days-9 (18.3%) Diagnosis of COVID-19 in patients with TB sequelae-7 (14.3%) Health workers involved -2 (4.1%) Mortality more in patients with TB sequelae due to older age group and associated comorbidities
.o	20 Male-12 (60%) Female- 8 (40%)	Pulmonary TB- 19 (95%) Associated Extra-pulmonary involvement- 3/19 Exclusive Extra-pulmonary involvement- 1 TB was diagnosed using Xpert MTB/RIF- 18(95%) Diagnosis confirmed by culture-14/18 (77.8%) Drug resistant TB- 5 BCG vaccination-3 Mortality- 1
G	3 (All males)	Past history of pulmonary TB taking anti-tubercular drug treatment in first and second case Untreated TB for 50 years- third case All were treated
C	3 (All males)	1st Case- Latent TB (IGRA+, Sputum for AFB -ve, Culture -ve) with COVID-19 2nd Case- Active Drug Resistant TB already on second line drugs with COVID-19 (IGRA+, sputum

		for AFB smear +, Culture +) Sputum for COVID-19 also positive 3rd case- Previous history of TB with IGRA + Diagnosis of COVID 19 with features of ARDS 3 days after admission All were treated
Y	13 (Gender profile not available)	Latent TB infection (IGRA +ve) with COVID-19:- 13 Latent TB infection with severe/critical COVID-19:-7 TB co-infection with disease severity (severe/critical 78% vs mild/moderate cases 22%; p=0.0049) Infection to development of symptoms (MTB+SARS-CoV-2: 6.5 ± 4.2 days vs SARS-COV-2: 8.9 ± 5.2 days; p=0.073) Symptom development to severe disease (MTB+SARS-CoV-2: 3.4±2.0 days vs SARS-COV-2: 7.5±0.5 days; p=0.075)
I	69 Cohort A-49 (71.1%) Cohort B-20 (28.9%) Male – 52 (75.4%) Female- 17 (24.6%)	Migrants: - 43/69 (62.3%) Cohort A: - 26/49(53.1%) Cohort B:-17/20 (85.0%) Mortality: - 8 / 69 (11.6%) Cohort A- 7 (14.3%) Cohort B- 1 (5%) TB diagnosed before COVID-19- 6 (8.7%) Post TB sequelae with COVID-19-1(1.5%) TB and COVID-19 diagnosed simultaneously-1(1.5%) Male/Female- 7 (14.3%) / 1 (5%) BCG vaccination-3 (37.5%) Pan-susceptible strains-7 (14.3%) *Mycobacterium bovis* intrinsically resistant to pyrazinamide-1 Migrants were younger and having lesser comorbidities as well as mortality compared to natives
	Single case Male	Low grade fever, cough with expectoration and breathlessness since 1.5 months COVID-19 RT-PCR + for severe acute respiratory infection

		Empirical anti-tubercular therapy started on non-resolving symptoms Died due to progressive illness Diagnosis of TB confirmed post mortem by positive CBNAAT
F	Single case Male	Hypertensive, Diabetic Recent onset fever, productive cough, chest pain, myalgia, fatigue and respiratory distress ? Past history of TB Unprotected contact with his cousin recently recovered from COVID-19 Findings of Acute hypoxemic respiratory failure with ARDS COVID-19 RT-PCR + CBNAAT of sputum detected concomitant infection with *Mycobacterium tuberculosis* sensitive to rifampicin Treatment with empiric therapy for COVID-19 and first line anti-tubercular drug Discharged and under regular follow up

Abbreviations used:- BCG- Bacillus Calmette-Guerin; CBNAAT- Cartridge Based Nucleic Acid Amplification Test ; COVID-19- Coronavirus Disease 2019 ; DR-TB – Drug-Resistant Tuberculosis; HIV- Human Immunodeficiency Virus ; IGRA- Interferon-Gamma Release Assay ; RT-PCR- Reverse Transcriptase- Polymerase Chain Reaction ; TB- Tuberculosis

Figures

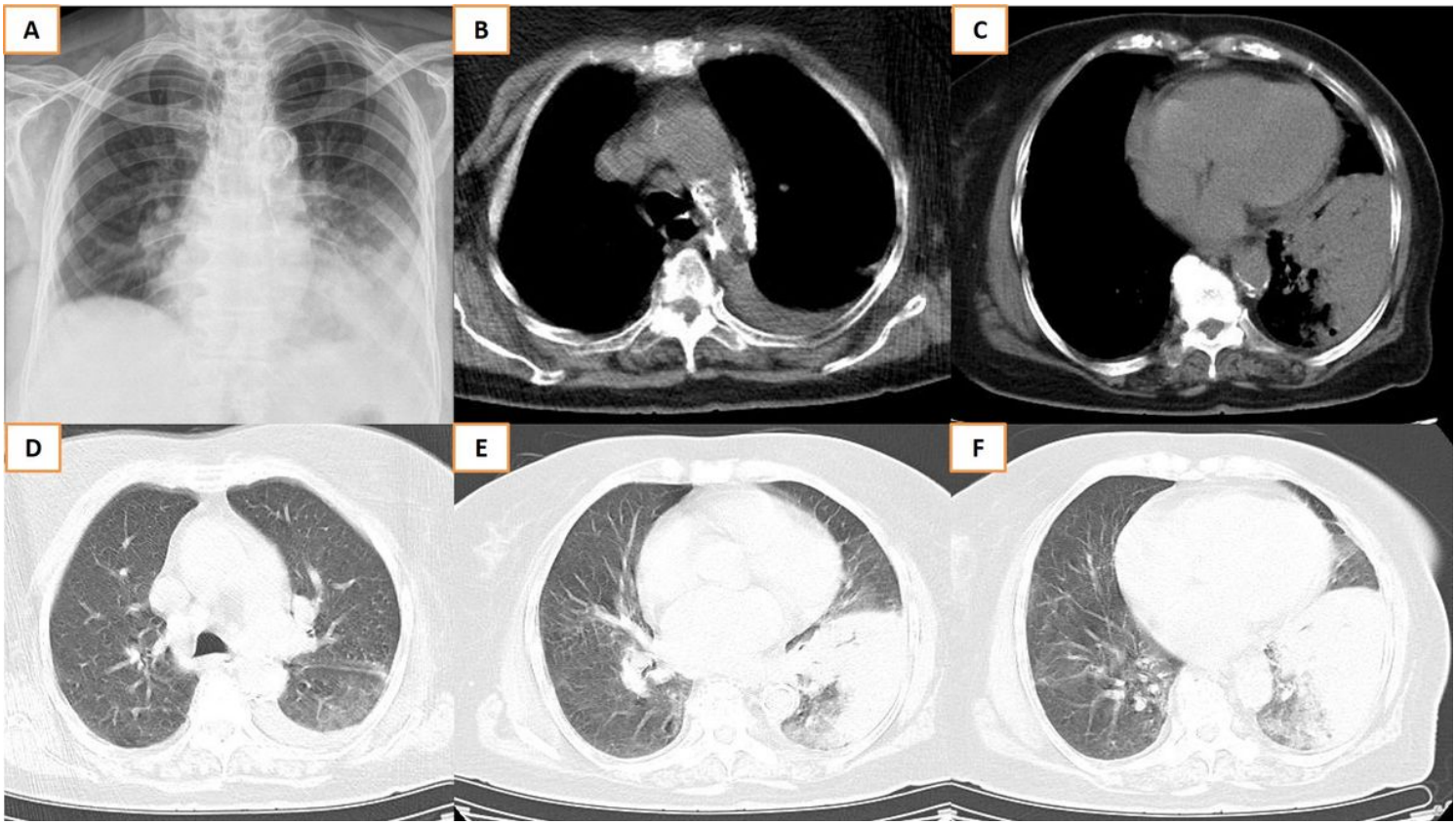

Figure 1

(A) Chest X-Ray showing left lower zone alveolar opacity likely consolidation ; (B-F) Computed tomography thorax (mediastinal and lung window) showing bilateral diffuse ground glassing and left lower lobe dense consolidation having air bronchogram with underlying effusion