CASE REPORT

# TWO CASES OF SARS-COV-2 AND MYCOBACTERIUM TUBERCULOSIS CO-INFECTION: DIAGNOSIS AND TREATMENT

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**Abstract.** Co-infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and tuberculosis (TB) is infrequent. Here, we report two patients diagnosed with coronavirus disease 2019 (COVID-19) pneumonia together with pulmonary TB. Patient 1 is a 70-year-old male with COVID-19 pneumonia with acute respiratory distress syndrome (ARDS) complication and pulmonary TB who received darunavir plus ritonavir, chloroquine and favipiravir for COVID-19 ARDS, and standard anti-TB agents were adjusted to non-rifampicin (levofloxacin) regimen to avoid drug-drug interaction between protease inhibitors and rifampicin. Patient 2 is a 56-year-old male with COVID-19 pneumonia and miliary TB who received hydroxychloroquine, azithromycin and favipiravir for COVID-19 pneumonia, and a standard short course of rifampicin-based regimen for miliary TB. Given the prevalence of TB in Thailand, determination of TB co-infection among COVID-19 patients should lead to favorable clinical outcomes.

**Keywords:** co-infection, COVID-19, SARS-CoV-2, tuberculosis

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## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused nearly 27 million confirmed cases of coronavirus disease 2019 (COVID-19) worldwide and 900,000 deaths as of 6 September 2020 (WHO, 2020a). In January 2020, Thailand was

the first country outside China to report a COVID-19 case (Pongpirul *et al*, 2020a). Bamrasnaradura Infectious Diseases Institute in Nonthaburi Province, Thailand was assigned as a hospital designated to this emerging infectious disease and, to date, has investigated more than 6,000 suspected COVID-19 patients and treated more than 190 cases (Pongpirul *et al*, 2020b).

The majority of co-infection between SARS-CoV-2 and other respiratory pathogens are viruses and bacteria (Lansbury *et al*, 2020). There are a few reports of tuberculosis (TB) and COVID-19 co-infection, but problems of possible drug-drug interactions in the treatment of both diseases have rarely been investigated (Motta *et al*, 2020). Thailand is one of the countries with high TB burden (WHO, 2019). Here, we present two patients diagnosed with COVID-19 pneumonia together with pulmonary TB and discuss how their clinical presentations impacted their respective medication.

## CASE REPORT

### Patient 1

A 70-year-old male bus driver with a history of contact with Chinese tourists presented with fever and dry cough during the preceding six days, then developed shortness of breath one day before hospitalization (3 February 2020). At the emergency room, Patient 1 reported drowsiness and marked dyspnea. Physical examination showed a respiratory rate of 28 breath/minute, heart rate of 110 beats/minute, blood oxygen saturation level ($SpO_2$) of 80% in room air and crepitation sound in both lungs. Patient 1 was intubated via an endotracheal tube. Chest radiograph (CXR) demonstrated diffuse fine granular opacities in both lungs, more on the right lower lung, and reticulonodular opacities in both upper lungs (Fig 1A). White blood counts were as follows: leukocyte count of 11,200/$mm^3$, 65% neutrophils, 8% lymphocytes, and 34% band form neutrophils. The ratio of arterial oxygen partial pressure ($PaO_2$) to fractional inspired oxygen ($FiO_2$) or $PaO_2/FiO_2$ was 130, consistent with moderate acute respiratory distress syndrome (ARDS) (ARDS Definition Task Force *et al*, 2012). Intravenous piperacillin-tazobactam 4.5 grams every 6 hours was initially prescribed for empirical treatment of severe bacterial pneumonia.

Endotracheal aspiration for gram stain bacteria, routine bacterial cultures, and multiplex RT-PCR assay for respiratory pathogens (the Fast Track Diagnostic Respiratory Pathogens 33 Kit; Fast Track Diagnostics, Junglinster, Luxembourg) produced negative results. Nasopharyngeal swab and sputum collected for SARS-CoV-2 RT-PCR detection performed at two laboratories: the Thai Red Cross Emerging Infectious Diseases Health Sciences Center, Faculty of Medicine, Chulalongkorn University, and the Department of Medical Sciences, Ministry of Public Health yielded positive results (Ct of *RdRp* and N gene are 23.57 and 23.3, respectively; negative Ct cut-off at 40). Sputum acid-fast stain was negative but sputum Gene X-pert assay (Cepheid, Sunnyvale, CA) revealed presence of *Mycobacterium tuberculosis* (MTB) complex. Subsequent culture of

sputum on Lowenstein-Jensen media (In-house preparation; Division of Tuberculosis, Department of Disease Control, Ministry of Public Health. Thailand) generated cultures of MTB complex (WHO, 1998).

Anti-tuberculosis agents (isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 1500 mg/day, and ethambutol 1000 mg/day) were prescribed. At that time, no treatment guideline was approved for treatment of COVID-19 pneumonia and only symptomatic treatment was given. On Day 3 post-admission, progressive dyspnea and desaturation were observed and CXR progressed to ground-glass opacities in both lungs (Fig 1B), with $PaO_2/FiO_2$ ratio of 100, compatible with severe ARDS (ARDS Definition Task Force *et al*, 2012). Darunavir 1200 mg/day plus ritonavir 200 mg/day and chloroquine 500 mg/day were prescribed on Day 4 post admission, together with convalescent plasma derived from a 51-year-old male, the first recorded case outside of china, and favipiravir 3200 mg on Day1, followed by 1200 mg/day were given on Days 7 and 13 for treatment COVID-19 severe ARDS, respectively. At the same time, anti-tuberculosis agents were adjusted to a non-rifampicin-based (levofloxacin 750 mg/day) regimen. Physical improvement was observed. On Day 22 post-admission, SARS-CoV-2 RT-PCR assay of nasopharyngeal swab and sputum produced negative results; all drugs were discontinued and the patient was placed on a standard short course of rifampicin-based anti-tuberculosis regimen. Unfortunately, Patient 1 developed ventilator-associated *Stenotrophomonas maltophilia* pneumonia compounded by acute renal failure resulting in death on Day 50 post-admission.

**Patient 2**

A 56-year-old male with alcoholic cirrhosis child B and known exposure to a relative with COVID-19 presented with weight loss of 5 kg over a period of one month, productive cough during the prior three weeks and fever and progressive dyspnea during the previous five days. On admission (1 April 2020), temperature was 37.9°C, respiratory rate of 18 breaths/minute and $SpO_2$ of 97% in room air.

Nasopharyngeal and throat swabs for SARS-CoV-2 RT-PCR assay (the COVID-19 Coronavirus Real Time PCR Kit; Jiangsu Bioperfectus Technologies Co, Ltd, Jiangsu, PR China) were positive (Ct of Orf1ab and N gene are 37.89 and 36.92, respectively; negative Ct cut-off at 40). CXR yielded diffuse fine reticulonodular opacities in both lungs, predominately at the left perihilar region and left lower lung, compatible with a miliary pattern (Fig 1C). Sputum acid-fast stain yielded positive result and MTB complex was also detected using Gene X-pert (Cepheid).

Hydroxychloroquine 500 mg/day, lopinavir 800 mg/day plus ritonavir 200 mg/day and azithromycin 250 mg/day were initially prescribed for COVID-19 pneumonia and a regimen of standard drugs for miliary TB. Favipiravir 3200 mg on Day 1 followed by 1200 mg/day was introduced in place of lopinavir/ritonavir on Day 2 post-admission. By Day 12 post-admission, Patient 2 chest symptoms had gradually resolved with

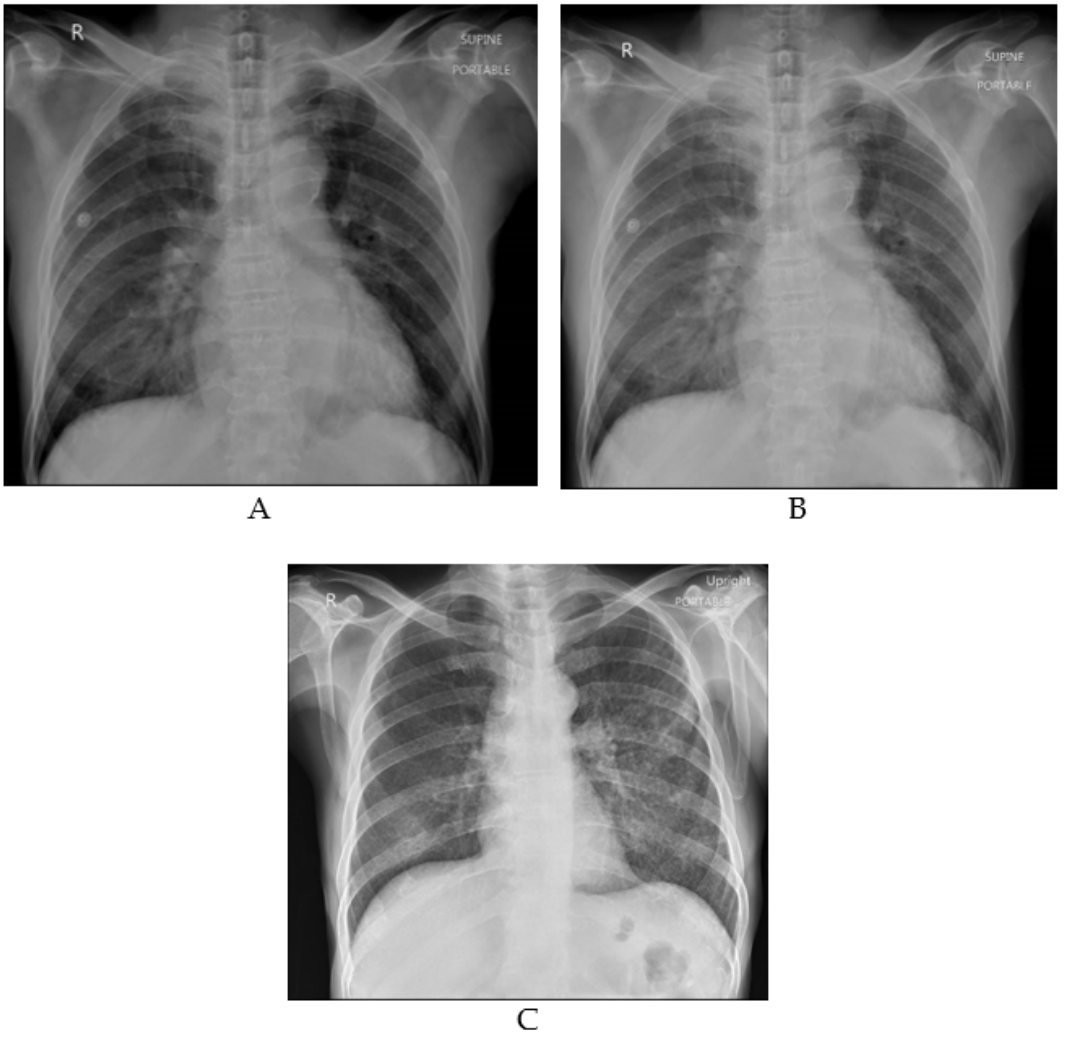


Fig 1 - Chest radiographs of Patient 1 (A and B) and Patient 2 (C)

A: Day 1 of admission showing diffuse fine granular opacities in both lungs, more on right lower lung and reticulonodular opacities in both upper lungs; B: Day 3 post-admission showing ground-glass opacities in both lungs; C: Day 1 of admission showing diffuse fine reticulonodular opacities in both lungs, predominately at left perihilar region and left lower lung, compatible with miliary pattern

defervescence. SARS-CoV-2 RT-PCR assay of nasopharyngeal and throat swabs were negative on Day 13 post-admission and the patient was discharged on Day 16.

## DISCUSSION

TB co-infection with severe acute respiratory syndrome (SARS) is transiently immunosuppressive and significantly causes lower mean number of CD4+ and CD8+ T cells, with poorer IgG antibody response that predisposes to new infection or reactivation of latent infection (Liu *et al*, 2006). Both COVID-19 and TB share similar poor prognostic factors, such as advanced age, diabetes mellitus and chronic lung disease (Fitzgerald *et al*, 2020; Wu and McGoogan, 2020). An observational case-control study reported both active TB disease and latent TB infection increase susceptibility to SARS-CoV-2 infection and related to COVID-19 severity (Chen *et al*, 2020). Preliminary analysis of deaths in 69 patients with TB and COVID-19 demonstrated mortality is likely to occur in elderly patients with co-morbidities, and TB might not be a significant determinant of mortality (Motta *et al*, 2020). Nonetheless, a larger study is necessary to evaluate interaction between COVID-19 and TB on disease severity and treatment outcome.

Although COVID-19 and TB both present with fever and respiratory symptoms, there are still several important clinical features to differentiate them, namely, in COVID-19, fever and cough can occur within a few days or a week of infection (Gandhi *et al*, 2020) while symptoms of TB typically develop with a gradual onset, mostly lasting weeks (Fitzgerald *et al*, 2020); dry cough is more common in uncomplicated COVID-19 (Gandhi *et al*, 2020) while productive cough is usually present in TB with hemoptysis (Fitzgerald *et al*, 2020); and shortness of breath develops early after onset of COVID-19 (Gandhi *et al*, 2020) but slowly progresses in pulmonary TB (Fitzgerald *et al*, 2020). ARDS is an unusual manifestation of pulmonary TB, with prevalence of ARDS secondary to pulmonary TB ranging from 1.3-1.5% (Kajeekul and Jitmuang, 2018). On the other hand, around 5-10% of COVID-19 patients require admittance to intensive care unit (Grasselli *et al*, 2020; Wu and McGoogan, 2020), with 88% requiring mechanical ventilation and develop severe ARDS (Grasselli *et al*, 2020).

The most common CXR and CT findings of COVID-19 are ground-glass opacities, consolidation, especially bilateral lower lobe consolidation, and peripheral lung opacities, which are markedly different from pulmonary TB (Jacobi *et al*, 2020). Miliary pattern in COVID-19 has not been reported to date, while main etiologies of miliary nodules are TB, fungal infection and bronchoalveolar carcinoma (Fitzgerald *et al*, 2020). Miliary infiltration in TB is one of the risk factors associated with mortality (Lin *et al*, 2014).

Rifampicin is the cornerstone for treatment of TB, but being a strong inducer of cytochrome P450 3A4, it can result in subtherapeutic levels and thereby compromising efficacy of other drugs, including protease inhibitors (PIs) (Fitzgerald *et al*, 2020). According to Thai public health guidelines,

darunavir or lopinavir/ritonavir (PIs) and chloroquine or hydroxychloroquine are recommended in mild COVID-19 pneumonia, with supplementation of favipiravir in severe pneumonia (DDC, 2020). Hence, we changed the standard anti-tuberculosis drugs to a non-rifampicin-based regimen to avoid drug-drug interactions if patients have COVID-19 and TB co-infection with ARDS. Meanwhile, if TB is the main problem that requires rifampicin, we discontinued boosted PIs and used other drugs instead.

There are still exist other concerns in the management of both diseases. Firstly, use of immunomodulators, such as dexamethasone or interleukin-6 inhibitors in moderate-to-severe COVID-19 may increase the risk of reactivation of latent TB infection or aggravate active TB disease (NIH, 2020). Thus, other immune-based therapies that do not affect host immunity such as convalescent plasma might be a more suitable adjunctive treatment. Secondly, hepatitis due to concurrent use of anti-TB drugs and antivirals (favipiravir, boosted PIs, and chloroquine) may occur and thus there is need to monitor results of liver function tests (NIH, 2020). Thirdly, precautions against contact and droplet infections are recommended for healthcare workers when caring for suspected or confirmed COVID-19 patients (WHO, 2020b). Precautionary measures against airborne transmission must be initiated where patients have TB co-infection.

In conclusion, in high TB burden settings, the possibility of TB co-infection among COVID-19 patients must be taken into consideration, especially among high-risk groups vulnerable to unfavorable outcomes. Early diagnosis of both TB and COVID-19 is of critical important in disease management resulting in appropriate treatment and favorable outcome.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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