Reactivation of Pulmonary Tuberculosis in a Patient With COVID-19

Case Report and Review of Literature

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Abstract: Given COVID-19 rise in populations with high burden of tuberculosis infection, the interplay between COVID-19 and tuberculosis reactivation needs further investigation. We report a case of a 64-year-old man who developed acute respiratory distress syndrome due to severe COVID-19 infection. He was managed with intubation, prone-position mechanical ventilation, inhaled nitric oxide, and methylprednisolone 40 mg intravenous twice daily for 5 days. He developed unexplained persistent fever and leukocytosis that failed to respond to empiric broad-spectrum antibacterial, antifungal agents, and a 3-day course of intravenous methylprednisolone 1000 mg for possible usual interstitial pneumonitis. His endotracheal aspiration samples tested positive for Mycobacterium tuberculosis, and antituberculosis regimen was started. The patient died as result of decision to withdraw life support. This report establishes the clinical picture of a tuberculosis reactivation in a COVID-19 patient. The complex interaction between COVID-19, steroids, and tuberculosis is a clinical dilemma of great significance.

Key Words: MeSH, COVID-19, SARS-CoV-2, novel coronavirus, tuberculosis reactivation, latent tuberculosis, steroids

Since its emergence in December 2019, the coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be associated with increasing worldwide death toll, which prompted the World Health Organization to declare an ongoing pandemic. Among the experimental treatments investigated in COVID-19 patients, steroids have been explored with great interest—in particular, the data from the RECOVERY trial demonstrated mortality benefit of dexamethasone in patients with severe form of COVID-19.

Although complications of COVID-19 associated with various morbidities continue to be investigated, there is a pressing need for studying the role of coinfection with pulmonary tuberculosis, given that there are rising numbers of COVID-19 infections in the countries where tuberculosis is highly prevalent. In this case report, we describe a patient infected with COVID-19 who experienced reactivation of latent pulmonary tuberculosis during hospitalization.

CASE REPORT

A 64-year-old man of East Asian descent was assessed by the COVID-19 center because his wife, an employee in a long-term care facility, tested positive. He had dyspnea and was found to be hypoxic with oxygen saturation of 85% on room air. His medical history included type 2 diabetes, hypertension, and dyslipidemia. He did not smoke, and review of systems was unremarkable. On arrival to the emergency department, his vitals were as follows: temperature, 37.1°C; heart rate, 132 beats/min; blood pressure, 134/78 mm Hg; respiratory rate, 35 breaths/min; and O2 saturation 94% on 50% fraction of inspired oxygen (FiO2) via venturi mask. His physical examinations were unremarkable. His initial chest radiography was unremarkable, and there were no prior abnormal reports available. His nasopharyngeal swab, however, came back positive for COVID-19.

Initially, he remained relatively stable, but his O2 requirements fluctuated, often requiring as high as 80% FiO2 via high flow nasal cannula. On day 9 of the hospital admission, he started having respiratory distress with O2 saturation of 88% and PO2 of 48 mm Hg despite being on 90% FiO2 via high flow nasal cannula. He was intubated and ventilated in accordance with adult respiratory distress syndrome lung protection strategy. Prone ventilation was used almost throughout the intensive care unit course to maintain PaO2/FiO2 > 150 for 16 hours a day. We used inhaled nitric oxide of 20 ppm for a PaO2/FiO2 ratio <80, as he was not eligible for extracorporeal membrane oxygenation. Also, intravenous methylprednisolone 40 mg twice daily was administered for 5 days starting on day 14 as part of severe adult respiratory distress syndrome management. His admission was complicated by acute renal failure (managed with intermittent hemodialysis), bacteremia, and ventilator-associated pneumonia due to Klebsiella pneumoniae, which were appropriately treated with intravenous ceftriaxone. On day 35, he developed persistent fever and leukocytosis up to 40,000 with left shift that failed to respond to empiric broad-spectrum antibacterial and antifungal agents. Vigorous diagnostic workup was performed. Repeat COVID-19 polymerase chain reaction from nasopharyngeal swab and endotracheal tube yielded a negative result.

Chest computed tomography showed subpleural and interlobular thickening with honey combing, ground-glass opacities, and traction bronchiectasis (Fig. 1). Bronchoscopy revealed diffuse bronchiitis with friable mucosa throughout the lung and thick white colored mucus plugging in the right lung. Blood cultures, bronchoalveolar lavage bacterial and fungal culture, and multiplex polymerase chain reaction for respiratory viruses including SARS-CoV-2 and urine legionella antigen showed negative results. On day 40, a pulse steroid with intravenous methylprednisolone 1000 mg daily was administered for 3 days for possible usual interstitial pneumonitis without improvement. Since the patient was born in the Philippines, an endotracheal aspiration was sent for acid-fast bacilli smear and culture. Both acid-fast smear and nucleic acid amplification test were positive for Mycobacterium tuberculosis. There was no documentation of tuberculosis history or abnormal results of tuberculosis skin or quantiferon testing. He was treated withisoniazid, rifampicin, pyrazinamide, and ethambutol. On day 47 in the intensive care unit, the patient died after discussion with the family who agreed to treatment.
His endotracheal aspiration culture grew *M. tuberculosis* that was susceptible to both isoniazid and rifampicin.

**DISCUSSION**

Reactivation of latent tuberculosis is one of the main reasons for active tuberculosis in the world. It is estimated that in 2017, active tuberculosis killed 1.6 million people. Although the mechanism of reactivation of tuberculosis is still under investigation, it is conceptualized that in healthy patients, a robust immune response is able to form granulomas that prevent development of active tuberculosis, whereas in patients with dysregulated immunity, the reactivation of tuberculosis happens. Several high-risk factors for tuberculosis reactivation, such as human immunodeficiency virus co-infection, organ transplantation, tumor necrosis factor-α blockers, silicosis, close contact exposure, or chronic renal failure requiring dialysis, have been identified in the literature. A recent study involving COVID-19 patients in the Philippines demonstrated that having concurrent or past active tuberculosis was associated with 2.17 times increased risk of death. However, the role of COVID-19 in reactivation of tuberculosis is yet to be investigated.

Our patient had many risk factors for tuberculosis reactivation, which included being born in an endemic country for tuberculosis, diabetes mellitus, use of corticosteroids while in intensive care unit, acute kidney injury, and use of hemodialysis for more than 1 month. There is a possibility that COVID-19 infection could play a role in tuberculosis reactivation through many potential mechanisms such as lymphopenia, including the depletion of TH4 cells, T-cell exhaustion (defined as progressive loss of effector function due to prolonged antigen stimulation), and cytokine storm, eventually leading to immune dysregulation. In particular, reactivation of tuberculosis has been reported in a COVID-19 patient who was also treated with tocilizumab, which points to the potential role of interleukin-6.

With regard to the patient’s exposure to methylprednisolone, there are multiple case reports of tuberculosis reactivation.

![Image](https://example.com/image.png)

**FIGURE 1.** Nonenhanced CT chest on day 35 showing subpleural and interlobular thickening with honeycombing, ground-glass opacities, and traction bronchiectasis bilaterally.

**TABLE 1.** Literature Review of Case Reports That Describe COVID-19 Infection in Patients With Tuberculosis and Who Were Treated With Corticosteroids

| Authors          | Country     | Patient Demographics: Age/Sex | Comorbidities                              | Treated With Corticosteroids | Hospitalization, d | Tuberculosis Testing in Hospital. | Outcome     |
|------------------|-------------|-------------------------------|--------------------------------------------|-----------------------------|--------------------|----------------------------------|-------------|
| Faqihi et al14   | Saudi Arabia| 60 y/male                     | Hypertension and diabetes mellitus         | Yes                         | 27                 | NAAT-positive sputum              | Recovered   |
| He et al15       | China       | 67 y/male                     | Hypertension; latent tuberculosis          | Yes                         | 37                 | Not performed                    | Recovered   |
|                  |             | 26 y/male                     | None; latent tuberculosis                  | No                          | 28                 | Not performed                    | Recovered   |
|                  |             | 76 y/male                     | None; latent tuberculosis                  | Yes                         | 24                 | Not performed                    | Recovered   |
| Liu et al16      | China       | 48 y/male                     | None                                        | Yes                         | 14                 | IGRA positive. AFB and culture negative. | Recovered   |
|                  |             | 26 y/male                     | Multidrug–resistant active pulmonary tuberculosis | No                        | 14                 | IGRA, AFB, and culture positive | Recovered   |
|                  |             | 46 y/male                     | None                                        | No                          | 9                  | IGRA positive. AFB and culture negative | Recovered   |
| Yao et al17      | China       | 50 y/male                     | Ongoing treatment of pulmonary tuberculosis | Yes                         | 22                 | Sputum samples positive for AFB   | Died        |
|                  |             | 44 y/male                     | Diabetes mellitus                           | No                          | 26                 | Sputum and pleural smears negative for AFB | Recovered   |
|                  |             | 57 y/male                     | Diabetes mellitus; latent tuberculosis     | Yes                         | 27                 | Sputum positive for tuberculosis DNA | Recovered   |

AFB indicates acid-fast bacilli; IGRA, interferon-γ release assay; NAAT, nucleic acid amplification test.

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associated with steroids, such as treatments for autoimmune conditions,\textsuperscript{11} anaphylactic reactions,\textsuperscript{12} or nonmedical abuse.\textsuperscript{13} In Table 1, we summarize our literature review of case reports that describe COVID-19 patients with pulmonary tuberculosis, who also had treatment with corticosteroids. Because of insufficiency of data, definitive conclusion cannot be made about the role of corticosteroids in tuberculosis reactivation for COVID-19 patients.

If COVID-19 infection truly increases the risk of tuberculosis reactivation, the impact is projected to be dramatic in the developing countries and developed countries with foreign-born immigrants from tuberculosis-endemic countries. Given the recommendations from the RECOVERY trial,\textsuperscript{2} the burden of COVID-19 infection might be aggravated in these populations because of involvement of steroids in tuberculosis reactivation.

The degree of the pulmonary fibrosis and traction bronchiec-tasis observed in our patient can be explained by COVID-19 infection, as well as iatrogenic oxygen toxicity, ventilator-induced lung injury, and reactivation of pulmonary tuberculosis.\textsuperscript{18} This was considered a diagnostic challenge for our case because of the wide differential of chest computed tomography findings and absence of the typical findings of pulmonary damage in tuberculosis, such as adenopathy and cavitation.\textsuperscript{19}

**CONCLUSIONS**

COVID-19 can be associated with tuberculosis reactivation in patients with multiple risk factors, such as diabetes mellitus, renal failure, and steroid usage. We recommend screening and testing for tuberculosis in patients whose clinical status rapidly deteriorates or in patients who are candidates for treatment with steroids. We also recommend following up recovered patients from COVID-19 who received steroid therapy and giving them instructions about the warning signs of active tuberculosis. The current guidelines that support the use of dexamethasone in all COVID-19 patients who required O\textsubscript{2} therapy should address the potential risk of reactivation of tuberculosis with further research.

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