Reactivation of latent tuberculosis in a COVID-19 patient on corticosteroid treatment

Aviva Friedman , Katharine Claire DeGeorge

Family Medicine, University of Virginia Health System, Charlottesville, Virginia, USA

Correspondence to
Dr Aviva Friedman; ALYFRIEDMAN@GMAIL.COM

Accepted 29 April 2022

SUMMARY

Though the COVID-19 pandemic has made international headlines since 2020, behind the scenes, tuberculosis (TB) has remained a leading cause of global mortality. According to the WHO, TB is 1 of the top 10 causes of death globally, with about one-quarter of the world's population infected. This case report highlights a female patient who presented to the emergency department with signs and symptoms of COVID-19 and was admitted to hospital. When the patient demonstrated minimal clinical improvement after initiating treatment for COVID-19, further investigations uncovered concomitant reactivated TB. This case is helpful in underscoring the potential implications of the COVID-19 pandemic and current treatment guidelines on the global burden of TB, which could subsequently impact how practitioners approach screening and management of latent TB infection.

BACKGROUND

Tuberculosis (TB) has been a major focus of global public health initiatives since long before COVID-19 became a priority. It 1 of the top 10 causes of death globally, with one-quarter of the world's population infected and over 95% of cases found in low-income and middle-income countries.[1] This distribution of disease is also seen within the USA, where TB affects racial/ethnic minorities disproportionately; Hispanics, African Americans and Asians continue to have TB infections at higher rates than white, non-Hispanics.[2]

Unfortunately, the COVID-19 pandemic has reversed signifiant progress that had been made in the global fight against TB, causing many TB reduction targets to be missed.[3] In 2020, 10 million people became infected with TB and 1.5 million people died of it globally.[3] Data now show that from 2019 to 2020, there was an 18% decline in people newly diagnosed with TB, a decline back to 2012 levels, and reduced access to TB diagnosis and treatment led to an increase in deaths, back to 2017 levels.[3] This reduction in diagnosis and treatment is thought to be due to resource strain and difficulty seeking care in the midst of the COVID-19 pandemic and lockdowns, and though TB incidence had been downtrending since 2001 due to global health initiatives, these declines have mostly stopped, and a rise in global TB incidence is expected in 2022.[3]

The causative organism of TB is *Mycobacterium tuberculosis* (MTB), which is transmitted primarily by respiratory pathways.[4] While TB may initially present as a primary active infection, in patients with an adequate immune response, the disease may become contained and remain latent as TB infection (LTBI). For various reasons outlined below, LTBI may later become reactivated, also known as secondary TB.[4]

Approximately one-quarter of the global population is infected with LTBI, and is therefore at risk of reactivation.[1] Though widespread, however, LTBI can be diagnosed and treated; TB has an 85% treatment success rate.[5] The opportunity to intervene in the latent stage and mitigate the impact of this potentially fatal disease may become more pressing as COVID-19 coinfection becomes more common and persistent, particularly in areas of high TB prevalence. The prevalence of LTBI is also an important consideration when deciding on screening for LTBI and on COVID-19 treatment.

CASE PRESENTATION

A female patient in her 70s with a history of diet-controlled diabetes, chronic kidney disease and hypertension, presented to the emergency room (ER) of an academic hospital with signs and symptoms of COVID-19. These included fevers and chills, weakness, cough and diarrhoea. The patient had no known history of TB or exposures to TB since arrival to the US many years prior. It is not known if she was ever tested for TB on arrival to the USA. The patient had recently been diagnosed with COVID-19 pneumonia by nasopharyngeal PCR testing in the ER. At that initial visit, she had been discharged home from the ER and was being monitored with a hospital-provided home oxygen saturation monitoring system. The patient now presented with worsening shortness of breath and cough, pleuritic chest pain, dyspnoea on exertion and diarrhoea. Home monitoring showed oxygen desaturations to 85%, though the patient reported that weakness was her most significant symptom, and is what prompted her to present to the ER. In the ER, the patient continued to experience significant oxygen desaturations to the mid-80s with ambulation.

Labs were notable for a mild aspartate aminotransferase elevation and absolute lymphopenia, though they were otherwise grossly normal, with no elevation in brain natriuretic peptide, d-dimer or lactic acid. A chest X-ray confirmed diffuse bilateral lower lobe predominant heterogeneous airspace opacities, thought to represent viral pneumonia in the setting of known COVID-19 infection. The patient was admitted to the COVID-19 unit for monitoring, and shortly thereafter, she developed a new oxygen requirement of 2 L at rest. The

To cite: Friedman A, DeGeorge KC. *BMJ Case Rep* 2022;**15**:e247562. doi:10.1136/bcr-2021-247562

treatment protocol for hospitalised COVID-19 patients with an oxygen requirement at this hospital at the time of this patient's admission was a 5-day course of remdesivir, and a 10-day course of dexamethasone. These treatments were initiated on hospital day 1.

After admission, the patient's diarrhoea resolved and she reported that she no longer felt short of breath, however the patient was noted to have persistent dyspnoea on exertion and lethargy. No fever or night sweats were noted, and there is no record of weight loss or lymphadenopathy. By hospital day 4, the patient had shown minimal clinical improvement, and now required up to 7 L of oxygen. She received one dose of furosemide for presumed pulmonary oedema with interval improvement in her oxygen requirement to 4 L, but she rapidly reverted back to higher oxygen needs. A repeat chest X-ray was ordered to assess for signs of pulmonary oedema or worsening pneumonia. The chest X-ray showed minimal improvement of the pneumonia, but did demonstrate a new right apical opacity with central lucency, thought to represent a possible infection pneumatocele or underlying cavity due to a superimposed known viral infectious process. Radiology recommended a chest CT for further evaluation, which showed a right upper lobe multilobulated cavity communicating with a subsegmental bronchus, surrounded by centrilobular and tree-in-bud micronodules. These findings were noted to be highly concerning for reactivated TB.

Given this concern for reactivated TB, infectious disease (ID) was consulted. ID maintained a broad differential for this patient's CT findings, with consideration for endemic infections associated with her home country, a country with high TB prevalence, and her current residence in Virginia. Further workup was performed, including three respiratory acid-fast bacillus (AFB) specimens, each 8 hours apart, with MTB PCR ordered on two of these specimens to increase the specificity and sensitivity for TB. A quantiferon gold was collected, likely for consideration of treatment for LTBI if TB workup was otherwise negative. Other samples collected included sputum bacterial culture, fungal antigens, cryptococcal antigen, urine blastomyces antigen, urine histoplasma antigen, coccidioides antibody, HIV antibody, T-helper panel and strongyloides antibody, as steroids are considered to be a risk factor for strongyloides dissemination.

Two MTB PCR results returned positive on hospital day 6, confirming TB reactivation. 1+AFB was seen on two AFB smears. Bacterial culture grew 3+ white blood cells, 3+ mixed cells and 2+ normal oropharyngeal flora. Though the patient was on precautions for COVID-19, she was placed on airborne isolation. Labs were otherwise negative. She completed her courses of remdesivir and dexamethasone early in her hospitalisation as part of her COVID-19 treatment plan. Treatment was then initiated with RIPE therapy (rifampin, isoniazid, pyrazinamide and ethambutol) and the patient remained on isolation precautions until she demonstrated three consecutive negative AFB smears. The patient showed continued signs of clinical improvement, and eventually was weaned off oxygen prior to her discharge home. She was hospitalised for a total of 39 days, and was discharged with plans to complete a total of 2 months of RIPE therapy. This patient was not followed by the authors after discharge.

GLOBAL HEALTH PROBLEM LIST

- TB incidence has been declining globally but is expected to rise in light of the COVID-19 pandemic.
- Besides increasing barriers to TB testing and treatment, the COVID-19 pandemic may also contribute to increasing active TB incidence due to immunosuppression secondary to infection and treatment.
- COVID-19 and TB coinfection is a major global health concern.
- LTBI is highly prevalent and there are no clear screening protocols available. LTBI is treatable.

GLOBAL HEALTH PROBLEM ANALYSIS

While there is significant literature exploring the double burden of TB and COVID-19, few case reports have specifically examined LTBI reactivation in the setting of COVID-19 infection. One case in the journal *Respiratory Medicine Case Reports* examined a 40-year-old female COVID-19 patient who presented to hospital with respiratory symptoms and a normal chest X-ray, and was found several weeks later to have reactivated TB on repeat chest X-ray.[6] Given that her symptoms were mild, the patient was treated conservatively, and therefore, treatment did not play a factor in this case. The authors theorised that the CD4 +T cell depletion associated with COVID-19 may have factored into this case of LTBI reactivation. This is consistent with the knowledge that LTBI is reactivated in the setting of immunosuppression.[7]

Though minimal explanation was offered by radiology or ID as to why reactivation was suspected as opposed to primary TB in the case outlined above, it is the assumption of the authors that reactivation was the leading diagnosis given the timeline of events following initial normal imaging, and characteristic findings on repeat imaging. These findings include cavitation and localisation to the upper lobe, which have been considered more typical of secondary/reactivated TB, whereas primary TB has been thought to cause middle and lower lung field opacities, adenopathy and pleural effusions.[8] Of note, though historically, there were thought to be radiographically distinguishing features between primary and secondary TB, more recent evidence has suggested against this finding.[8] However, given radiology and ID's conclusions, this case was treated as, and will be discussed as, reactivated TB for the sake of this report.

In the case report presented in detail above, the patient presented with several risk factors for TB, including high-prevalence country of origin, history of diabetes and lymphopenia. However, in contrast to the case presented in *Respiratory Medicine Case Reports*, the patient was treated with a 10-day course of dexamethasone for COVID-19. Corticosteroid treatment is an independent risk factor for developing TB infection, likely due to the effect of steroids on cellular immune response, which is an important immune function for controlling TB.[9] This response includes depression of monocyte numbers and function, inhibition of T-cell activation and subsequent reductions in cytokine and other immune response, as well as peripheral lymphocytopenia due to redistribution of lymphocytes.[8] This increased risk for TB reactivation is an important consideration, as the current standard of care for hospitalised COVID-19 patients on oxygen supplementation includes dexamethasone or other equivalent corticosteroids.[10 11]

There are many known risk factors for reactivation, however, there is currently no standard screening protocol for TB. The US Preventive Services Task Force recommends screening high-risk populations for LTBI, given the accuracy of available screening tests.[12] In this context, high-risk populations include those from countries with increased TB prevalence or high-risk congregate settings (eg, shelters, prisons). The American Thoracic Society

further categorises those at risk to include people with chronic conditions, including diabetes and renal failure, among others.[13] The WHO also recommends screening high-risk groups in a systematic way, including contacts of people with TB and people living with HIV, and emphasises continuous monitoring and adjustment of screening tactics as risk groups change.[5] It is important to note that while immigrants and refugees are routinely screened for TB on entry to the USA, this may not apply to individuals who enter the country outside of the legal immigration system.[14]

LTBI is a screenable and treatable condition with potentially detrimental effects if reactivated. The WHO's End TB Strategy, formulated in 2015, aims to end the global TB epidemic by reducing TB incidence by 80% and TB deaths by 90% by the year 2030.[1] The UN has added additional targets, including treating 30 million people for LTBI between 2018 and 2022 (WHO).[1] These efforts have been complicated by the COVID-19 pandemic, which is thought to have led to a decrease in people seeking testing and treatment for TB.[15]

Given its high global prevalence and relatively high lifetime risk of reactivation, estimated to be 5%–10%, it is worth considering screening select populations for LTBI, especially in the context of the COVID-19 pandemic.[1] This case suggests that reactivation of LTBI in the setting of COVID-19 infection could be multifactorial, both due to innate immunosuppression and due to steroid-induced immunosuppression. As countries with high TB prevalence, including India and Brazil, become some of the hardest hit by the COVID-19 pandemic, potential coinfection may be factored into decisions on LTBI screening in high-risk patients and on COVID-19 treatment plans.

Learning points

- This case highlights the significant health impacts of reactivated latent TB infection (LTBI) in a critically ill COVID-19 patient.
- LTBI has a high global prevalence, and immunosuppression secondary to COVID-19 infection and its treatment options may increase the risk for LTBI reactivation.
- Increased screening for LTBI may reduce significant morbidity and mortality associated with the disease, particularly in the context of the COVID-19 pandemic.

Twitter Katharine Claire DeGeorge @evidentlymd

Contributors AF performed literature search and writing of case report. KCD reviewed case and edited report.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iDs
Aviva Friedman http://orcid.org/0000-0001-7450-412X
Katharine Claire DeGeorge http://orcid.org/0000-0002-1708-2861

REFERENCES

1 Tuberculosis (TB). World Health organization, 2020. Available: https://www.who.int/news-room/fact-sheets/detail/tuberculosis [Accessed 12 Jun 2021].
2 Health disparities. centers for disease control and prevention., 2020. Available: https://www.cdc.gov/tb/topic/populations/healthdisparities/default.htm [Accessed 12 Jun 2021].
3 Global tuberculosis report 2021. World Health organization, 2021. Available: https://www.who.int/publications/digital/global-tuberculosis-report-2021/tb-disease-burden/incidence
4 Flynn JL, Chan J. Tuberculosis: latency and reactivation. *Infect Immun* 2001;69:4195–201.
5 The end TB strategy. World Health organization, 2020. Available: https://www.who.int/tb/strategy/en/ [Accessed 12 Jun 2021].
6 Khayat M, Fan H, Vali Y. COVID-19 promoting the development of active tuberculosis in a patient with latent tuberculosis infection: a case report. *Respir Med Case Rep* 2021;32:101344.
7 Ai J-W, Ruan Q-L, Liu Q-H, *et al*. Updates on the risk factors for latent tuberculosis reactivation and their managements. *Emerg Microbes Infect* 2016;5:e10.
8 Geng E, Kreiswirth B, Burzynski J, *et al*. Clinical and radiographic correlates of primary and reactivation tuberculosis: a molecular epidemiology study. *JAMA* 2005;293:2740.
9 Jick SS, Lieberman ES, Rahman MU, *et al*. Glucocorticoid use, other associated factors, and the risk of tuberculosis. *Arthritis Rheum* 2006;55:19–26.
10 Adarsh Bhimraj* RLM. COVID-19 guideline, part 1: treatment and management. IDSA home, 2020. Available: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ [Accessed 12 Jun 2021].
11 World Health Organization, 2020. Available: https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1 [Accessed 12 Jun 2021].
12 US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, *et al*. Screening for latent tuberculosis infection in adults: US preventive services Task force recommendation statement. *JAMA* 2016;316:962.
13 Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161:S221–47.
14 Medical examination: Frequently asked questions (faqs) [Internet]. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention, 2021. Available: https://www.cdc.gov/immigrantrefugeehealth/about/medical-exam-FAQs.html#me-3
15 Louie JK, Reid M, Stella J. A de[] pandemic. *Int J Tuberc Lung Dis* 2020;24:860–2.