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LETTER

Severe COVID-19 cases with a history of active or latent tuberculosis

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Dear Editor,

The global COVID-19 pandemic has already resulted in more than 5 million cases and > 300,000 deaths.[1] Five of the 55 COVID-19 patients (diagnosed according to the national COVID-19 guidelines[2]) treated in Shenyang, Liaoning Province, China, developed acute respiratory distress syndrome (ARDS; arterial oxygen partial pressure to fractional inspired oxygen ratio [PaO_2/FiO_2] ≤ 300 mmHg). Given the

possibility of coinfection with other respiratory pathogens showing similar symptoms (such as SARS and H1N1 influenza), the relatively high rates of latent TB infection (LTBI) in China (16–18% in rural China),[3] and the need to rule out TB infection prior to considering glucocorticoid therapy, we screened these patients for *Mycobacterium tuberculosis* using interferon-gamma release assays (IGRAs). All clinical specimens from suspected COVID-19 patients were sent for SARS-CoV-2 testing using reverse transcription polymerase chain reaction (qRT-PCR)[4,5] at the Shenyang Disease Control Center, and IGRA assays were performed in-house using X.DOT-TB ELISpot kits (TB Healthcare, Foshan, China).[6] Three IGRA-positive cases were identified, and acid-fast bacilli (AFB) sputum smears and bacterial culture (MGIT™960™; BD, Franklin Lakes, NJ, USA) were then performed using standard microbiological methods. Here, we report symptom development, disease progression and treatment for these three cases, each representing a different TB scenario.

Case 1

A 48-year-old male taxi-driver presented with an 18-day history of fever, fatigue, dyspnoea and cough. One week before symptom onset, this patient had contact with a relative who later developed COVID-19 symptoms. He was treated unsuccessfully with dexamethasone (20–25 mg daily) and azithromycin (intravenous [IV] drip) at a private clinic for 2 weeks. On admission, he appeared confused and anxious, showing signs of respiratory distress, hypoxia, sepsis and haemoptysis (respiratory rate [RR]: 45 breaths/min, SpO_2: 55–65%, PaO_2/FiO_2: 55 mmHg). He had a very low peripheral blood lymphocyte count (0.33 x 10^9/L), and low cellular immunity ($CD3^+$ 287/μL, $CD3^+CD4^+$ 162/μL, $CD3^+CD8^+$ 122/μL). A chest computed tomography (CT) scan showed large ground glass opacities in both lungs and a large area of mediastinal emphysema (Figure 1A). The patient was IGRA-positive, and sputum was SARS-CoV-2-positive, AFB smear-negative and culture negative. *Aspergillus fumigatus* was detected in sputum submitted for PMSeq® (BGI, Shenzhen, China) testing. As this critically ill patient had mediastinal emphysema, we provided extracorporeal membrane oxygenation (ECMO) support and haemoperfusion. To

block SARS-CoV-2, combat sepsis and improve his immune response we administered the following: the antiviral Arbidol (0.2 g thrice daily, oral; Shisiyao, Shijiazhuang, China), the antibiotics, moxifloxacin (0.4 g daily IV drip) and linezolid (0.6 g twice daily IV drip), the antifungal caspofungin (100 mg, daily IV drip) and immunomodulatory therapy with thymopentin (10 mg daily intramuscular). Although LTBI was detected, no preventive anti-TB therapy was given. After 2 weeks, the patient's condition stabilised and he was discharged.

Case 2

A 26-year-old male with multidrug-resistant (MDR) TB presented with a 2-week history of cough associated with shortness of breath and fever. The patient was diagnosed with culture-confirmed pulmonary TB in 2013. Poor compliance to the standard anti-TB regimen (due to adverse drug reactions and suboptimal clinical response) led to disease relapse in December 2018. This was confirmed with chest radiographs and clinical symptoms consistent with active pulmonary TB, and phenotypic drug susceptibility testing indicated rifampicin and isoniazid resistance. His TB treatment regimen was therefore adjusted appropriately (ethambutol, pyrazinamide, amikacin and levofloxacin). On admission in 2020, he appeared cachectic, with respiratory distress, hypoxia and haemoptysis (heart rate: 107 beats/min, RR: 35 breaths/min, blood pressure: 150/90 mmHg, partial pressure of oxygen [PO_2]: 55 mmHg, PaO_2/FiO_2: 131 mmHg). Chest CT scan showed a small ground glass opacity in the upper left lobe, and ground grass opacities, air space consolidations and peripheral linear opacities in the upper right lobe (Figure 1B). The patient was IGRA-positive, and his sputum was SARS-CoV-2-positive, AFB smear-positive and culture-positive. He was given nasal high-flow oxygen therapy (HFNC) (oxygen concentration 90%, flow rate 30 L/min), Arbidol and moxifloxacin (0.4 g daily oral administration), linezolid (0.6 g daily oral), cycloserine (0.25 g twice daily oral), clofazimine (0.1 g daily oral) and pyrazinamide (0.5 g thrice daily oral). The patient’s condition stabilised after 2 weeks and he was discharged to continue anti-TB treatment.

Case 3

A 46-year-old corporate manager presented with a 13-day history of fever and myalgia. He had travelled by train to Xinyang, Henan Province (bordering Hubei Province), 5 days before developing a fever, myalgia, sore throat, right chest pain and dyspnoea. Chest CT scan showed multiple patchy shadows, cords and ground glass density shadows in both lungs (Figure 1C–D). Adhesions and partial calcification, suggestive of right subpulmonary lesions and pleural TB scars, were observed. He tested IGRA-positive for *Mycobacterium tuberculosis* infection but was AFB smear-negative and culture-negative. The patient recalled taking antibiotics for pleural effusion and suspected tuberculous pleuritis as a teenager (his father had TB) but had no further anti-TB treatment due to financial circumstances. Pharyngeal swabs tested positive for SARS-CoV-2 on Day 3 after admission, and he developed ARDS (PaO_2/FiO_2 260 mmHg). He was given HFNC and treated with Arbidol and moxifloxacin. As the TB lesions in his right lung and pleura were stable without anti-TB treatment, and COVID-19 symptoms had resolved, he was discharged after 9 days.

These cases of severe COVID-19 and TB with acute respiratory distress highlight the importance of determining if latent or active TB is a complicating factor in COVID-19 patients. During the SARS epidemic, hospitalised TB patients infected with SARS-COV-1 were considered at higher risk of death.[7] Host immune responses for clearing pathogens are stimulated on TB infection,[8] and SARS-CoV infection may further increase the immune burden, leading to an 'out-of-control' immune system and 'cytokine storms', ultimately inducing pulmonary and other organ dysfunction.[9]

The use of corticosteroids for treating lung inflammation is contentious.[10] While short-term use of low–moderate doses (≤0.5 mg/day/kg) has been recommended for treating severely ill COVID-19 patients,[11] our recommendation is not to administer corticosteroids when there is TB coinfection. As COVID-19 and TB disease may both cause immunosuppression, we recommend using immunomodulatory therapies such

as thymosin in patients with progressively lower lymphocyte counts. This approach was effective in Case 1, but its wider application needs further confirmation.

Complications observed here included severe mediastinal emphysema and a fungal infection (Case 1), and haemoptysis, possibly due to the use of ECMO (Case 1), or to pulmonary TB-associated cavity disease (Case 2). While precise consequences of *M. tuberculosis*/SARS-CoV-2 coinfection are unclear, physicians should prepare for complications such as haemoptysis, pneumothorax, mediastinal emphysema and fungal infections.

Infection control management also deserves attention. The presence of other infectious diseases, especially TB, should be evaluated carefully. Respiratory tract specimens should be checked repeatedly in IGRA-positive patients with lung shadows and typical pulmonary TB symptoms. If active TB is confirmed, patients should be isolated to avoid nosocomial transmission of TB. Screening for drug resistance should be performed and appropriate anti-TB treatment given. Case 1 (with LTBI) and Case 3 (with stable TB lesions) were not isolated or given preventive anti-TB therapy due to the potential for adverse reactions to anti-TB drugs. Whether SARS-CoV-2 infection increases the risk of individuals with LTBI developing active TB is an important issue that will require analysis. We have highlighted these cases to provide guidance for medical professionals in other high TB burden countries facing the COVID-19 pandemic.

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Conflicts of interest: none declared.

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FIGURE LEGEND

Figure 1 **A)** Case 1. Chest CT scan showing large ground glass opacities in both lungs and a large area of mediastinal emphysema. **B)** Case 2. Chest CT scan showing a small ground glass opacity in the upper left lobe and ground glass opacities, air space consolidations and peripheral linear opacities in the upper right lobe. **C and D)** Case 3. Chest CT scan showing multiple patchy shadows, cords, and ground glass shadows under the pleura in both lungs. Dilated bronchioles can be seen in some consolidation shadows (left panel), and spotted calcifications can be seen in the right lower lungs. Thickening of the right pleura can be seen, along with adhesions and partial calcification (right panel). CT = computed tomography.