

COVID-19 in tuberculosis patients: A report of three cases

To the Editor,

The World Health Organization declared the outbreak of novel coronavirus disease 2019 (COVID-19) a Public Health Emergency of International on 30 January 2020.¹ It is well documented that certain viral infections, such as measles, have been known to aggravate pulmonary tuberculosis (PTB), presumably as a result of depressed cellular immunity.^{2,3} Despite their vulnerability as a population, to date, most studies have focused on COVID-19 infection in patients without current respiratory disease. The clinical features and treatment of tuberculosis (TB) patients with COVID-19 are unclear and understudied. To the best of our knowledge, the coinfection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and *Mycobacterium* TB has not been reported previously. Therefore, we provide information and experience with the treatment of TB cases with confirmed COVID-19 infection.

Data were derived from 139 confirmed cases, which were hospitalized in Wenzhou Sixth People's Hospital from 17 January to 6 March 2020. Three TB cases with COVID-19 infection were confirmed by a real-time fluorescence polymerase chain reaction assay. All three patients were males, ages 26 to 76 years, and were prospectively followed from hospital admission to discharge.

Table 1 illustrates the clinical features, laboratory tests, clinical prognosis, treatments, and outcomes of the three patients. According to this epidemiological investigation, all patients were in close contact and infected from others with confirmed infections of COVID-19. Patients 1 and 2 had PTB history and were administered quadruple antituberculosis therapy, while patient 3 had untreated TB for 50 years. The cavitating lesion of patient 3 in the right upper lobe remained unchanged for many years. Considering the harmfulness of the SARS-CoV-2 specimen, the hospital restricted the examination of sputum Xpert, T-SPOT.TB, the culture of *Mycobacterium* TB, and so forth. The onset of their symptoms varied from a dry cough to chest tightness to persistent fever. Other symptoms included chest pain, diarrhea, and dyspnea. Patients 1 and 3, who were of older age, had hypoxemia and developed a critical type and severe type of COVID-19, respectively. Laboratory tests showed all of them had low lymphocyte count and increased levels of C-reactive protein, lactic dehydrogenase, and erythrocyte sedimentation rate. Computed tomography (CT) scans showed all of the cases presented with

multiple bilateral ground-glass opacities and consolidation, with air bronchogram.

All the patients had antiviral therapy including lopinavir, ritonavir, and arbidol with a long prognosis. Patient 1 progressed to respiratory failure type 1 and acute respiratory distress syndrome (ARDS) on day 10 after onset. He had treatment of noninvasive ventilation support. Both patients 1 and 3 were severe cases and had treatment of methylprednisolone. Since patient 3 had untreated TB for many years, he received antituberculosis therapy combined with glucocorticoid therapy. Cases 1 and 3 both had glucose level abnormalities and bacterial infections. They were put on antibiotic therapy and the symptoms relieved later. Patient 2 developed skin rashes with pruritus all over his body, which is considered an adverse reaction of the antiviral treatment. His symptoms improved after he stopped the antiviral therapy. All of the patients recovered and were discharged from the hospital. However, on a ninth day after discharge, patient 2 had a positive recurrence of SARS-CoV-2 RNA and returned to the hospital to remain in isolation and under observation.

Among these three COVID-19 combined patients with TB, two who were older in age developed severe cases of COVID-19 and one which was ARDS. All had a long recovery and it was difficult to resolve the problem of low Oxygenation Index. The CT images showed the COVID-19 lesions and TB lesions coexist and performed differently (Figure 1 and Figure S1). The COVID-19 lesions were mainly performed as ground-glass lesions and consolidation, mainly located in the peripheral zone. *Mycobacterium* TB lesions were mainly performed as a stripe of high-density shadow with a cavitating lesion, mainly located in the upper lung. Limited by the small sample size, we cannot draw the conclusion. Future large sample-sized study address on the pathology of COVID with CT imaging are warranted.

TB is the type of infection that requires cellular immunity, and nearly 100 years ago lung function studies with TB showed evidence of restrictive lung disease. In patients infected with *Mycobacterium* tuberculosis, whether treated or untreated, a variety of pulmonary and extrapulmonary sequelae and complications can occur, which include bronchiectasis, tracheobronchial stenosis, and broncho-lithiasis.⁴ Structural changes lead to obstructive, restrictive, or mixed patterns of impaired pulmonary function. Studies in patients with PTB have demonstrated that 33.3% to 94.0% of such patients develop the impaired pulmonary function.⁵ The risk factors for TB

TABLE 1 Clinical features, laboratory tests, clinical prognosis, treatments, and outcomes of the three patients

	Patient number		
	1	2	3
Age, y	67	26	76
Sex (M/F)	M	M	M
BMI	24.2	28.73	17.96
Past history	TB (treated 6 y ago) HBP	TB (treated 2 y ago)	TB (for 50 y, nontreated) Exfoliative dermatitis Arthrolithiasis
Smoking history	+	-	+
Imported case from Wuhan	+	+	-
Clinical features			
Fever (T_{max} , °C)	38.9	38.2	38.9
Dry cough	+	+	+
Chest tightness	+	-	+
Chest pain	-	-	+
Dyspnea	+	-	+
Diarrhea	-	+	-
Family cluster	+	+	+
Oxygen saturation on room air (%)	89↓	97	96
Respiratory rate	22	19	20
Laboratory findings			
Lowest leukocyte count ($\times 10^9/L$)	3.3↓	3.2↓	3.9↓
Lowest lymphocyte count ($\times 10^9/L$)	0.5↓	0.8↓	0.3↓
Lowest PaO ₂ , kPa	6.7↓ (FiO ₂ 33%)	NA	9.3↓ (FiO ₂ 33%)
Highest serum ALT, U/L	39	33	22
Lowest serum ALB, g/L	32.5↓	43.9	31.6↓
Highest serum CKP, U/L	142	41.1	105
Highest serum LDH, U/L	396↑	372↑	328↑
Highest CRP, mg/L	124.2↑	29.2↑	77.1↑
Highest ESR, mm/h	91↑	NA	38↑
Radiological findings of the thorax (radiograph/computed tomography)			
Initial change	Multiple bilateral mass ground-glass opacities, stripe of high-density shadow on right upper lobe (day 7)	Multiple ground-glass opacities on lower lobe bilaterally, with mediastinal lymphadenopathy (day 9)	Pathy ground-glass opacities on left lower lobe, stripe of high-density shadow on right upper lobe with a cavitating lesion in the upper lobe of the right lung (day 2)
Progressive change	Increased bilateral multiple ground-glass opacities and consolidation (day 13) Absorption of some area (day 18) Absorption than day 18 (day 24) Unchanged image (day 35) Absorption of some area (day 40)	Absorption of the ground-glass opacities (day 20) Absorption of some area (day 43)	Increased multiple ground-glass opacities and consolidation on lower lobe bilaterally (day 5) Absorption of some area (day 10) Increased consolidation (day 15) Increased consolidation (day 22) Absorption of some area (day 28)
Comorbid conditions			
Hyoxemia	+	-	+
Glucose level abnormal	+	-	+
ARDS	+	-	-
Bacterial infection	+	+	+
Medicine rash	-	+	-

(Continues)

TABLE 1 (Continued)

	Patient number		
	1	2	3
Treatment and outcome			
Aerosol therapy with interferon alfa-2b	+	+	+
Antivirus medicine	Lopinavir + Ritonavir Arbidol	Lopinavir + Ritonavir Arbidol	Lopinavir + Ritonavir Arbidol
Methylprednisolone	+ (day 10-11)	-	+ (day 5-12)
Antibiotics	+	+	+
Antituberculosis	-	-	+
Probiotics	+	+	+
Traditional Chinese medicine	+	+	+
Intravenous immunoglobulin	+	-	+
Ventilatory support	Noninvasive ventilation	-	Nasal cannula
Maximum oxygen requirement (FIO ₂)	50%	-	41%
Outcome of symptoms	Relief Last OI 325	Relief	Relief Last OI 396
Hospital stay, d	37	28	24

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; BMI, body mass index; CKP, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HBP, high blood pressure; LDH, lactic dehydrogenase; NA, not applicable; OI, Oxygenation Index = PaO₂/FIO₂; TB, tuberculosis.

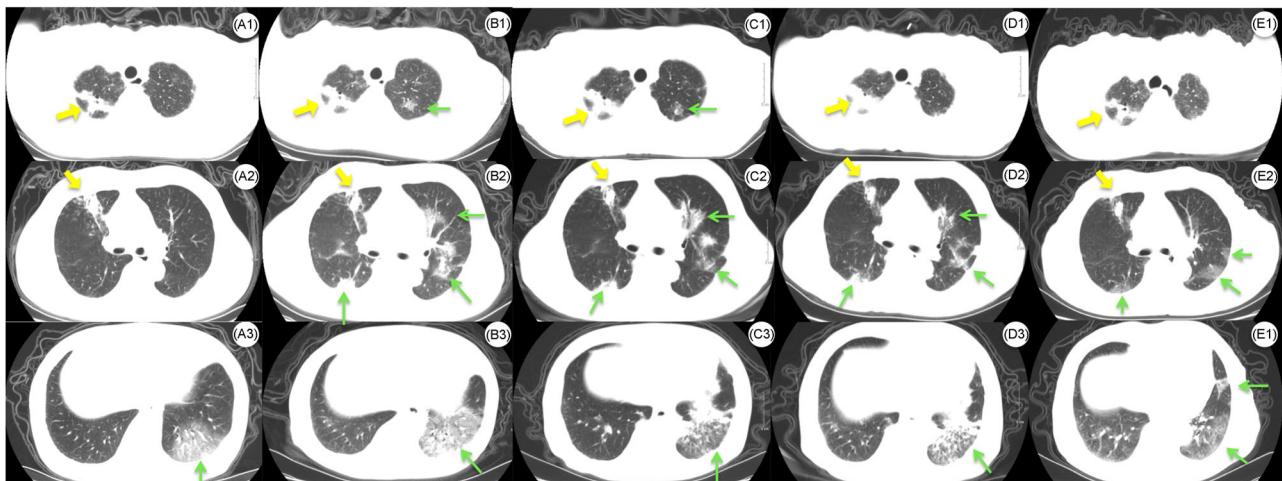


FIGURE 1 Axial CT images of the chest in patient 3 with the COVID-19 and tuberculosis coinfection. A, CT obtained on day 2. A1, Stripe of high-density shadow with a cavitating lesion in the right upper lobe. A2, Stripe of high-density shadow in the right upper lobe. A3, Pathy ground-glass opacities (GGOs) in the left lower lobe. B, CT obtained on day 7. B1, Stripe of high-density shadow with a cavitating lesion in the right upper lobe, slight GGO in the left upper lobe. B2, Stripe of high-density shadow on the right middle lobe, subpleural (GGOs) in the right upper lobe. Multifocal, limited GGO is seen in the left lungs. B3, Increased multiple GGOs and consolidation in the left lower lobe with air bronchograms. C, CT obtained on day 16. C1, Stripe of high-density shadow with a cavitating lesion in the right upper lobe, slight GGO in the left upper lobe. C2, Stripe of high-density shadow on the right middle lobe, absorption of GGO bilaterally. C3, GGO and consolidation in left lower lobe. D, CT obtained on day 22. D1, Stripe of high-density shadow with a cavitating lesion in the right upper lobe, absorption of GGO bilaterally. D2, Stripe of high-density shadow on the right middle lobe, absorption of GGO bilaterally. D3, GGO and consolidation in left lower lobe. E, Follow-up CT obtained on day 59. E1, Stripe of high-density shadow with a cavitating lesion in the right upper lobe. E2, Stripe of high-density shadow on right middle lobe, absorption of GGO bilaterally. E3, Absorption of GGO in the left lower lobe. Yellow arrows demonstrated the lesion of tuberculosis. Green arrows demonstrated the lesion of COVID-19. COVID-19, coronavirus disease 2019; CT, computed tomography

patients with reduced pulmonary function are having previously had culture-positive PTB, being over 50 years of age, having a low level of education, and having experienced recurrence of TB.⁶ This study suggests that previous lung disease such as treated or untreated mycobacterium TB and old age are independent risk factors of a worse prognosis of those infected with COVID-19. Using a glucocorticoid for a short period of time in the early stages of prognosis could reduce the inflammation, but longer term usage could result in the risk of bacterial infections and abnormal glucose levels. These case reports remind us of the importance of strict isolation of patients with COVID-19, careful use of steroids for their case management, and the possibility of coinfection with TB in COVID-19 patients with incomplete recovery.

The presented case series demonstrates PTB patients with COVID-19. In this study, elderly patients with TB easily progressed to the severe type of COVID-19 and had a long recovery process. These case reports remind us of the possibility of coinfection with TB in COVID-19 patients with incomplete recovery, as well as the importance of careful use of steroids for their case management.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.


AUTHOR CONTRIBUTIONS

GH and JC conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript. WS conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. JS and JD collected data, and reviewed and revised the manuscript. JW carried out the analyses, critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript. XJ and MG carried out the analyses, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICS STATEMENT

This study was approved with the written consent by the Ethics Committee of Wenzhou Central Hospital (No. L2020-02-004X).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.