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Guiging He

Jing Wu

Jichan Shi

Michelle Gamber

Xiangao Jiang

See next page for additional authors

Authors

Guiging He, Jing Wu, Jichan Shi, Michelle Gamber, Xiangao Jiang, Wenjie Sun, and Jing Cai

Jing Wu ORCID iD: 0000-0002-1224-0912

Wenjie Sun ORCID iD: 0000-0002-2608-9037

Jing Cai ORCID iD: 0000-0003-3609-4291

COVID-19 in Tuberculosis patients: a report of three cases

Guiqing He [1, 2‡], Jing Wu [3‡], Jichan Shi [4‡], Jianyi Dai[5‡], Michelle Gamber[6], Xiangao Jiang [7*], Wenjie Sun [8,9*], Jing Cai [10*]

1. Department of Infectious Diseases, Wenzhou Sixth People' s Hospital, Wenzhou Central Hospital Medical Group, Wenzhou, 325000 China

2. Infectious Diseases Laboratory, Wenzhou Sixth People's Hospital, Wenzhou Central Hospital Medical Group, Wenzhou, 325000 China; hegq123@126.com

3. Department of Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, 200040 China; jingee@fudan.edu.cn

4. Department of Infectious Diseases, Wenzhou Sixth People' s Hospital, Wenzhou Central Hospital Medical Group, Wenzhou, 325000, China; shijichan@163.com

5. Department of Infectious Diseases, Wenzhou Sixth People' s Hospital, Wenzhou Central

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Hospital Medical Group, Wenzhou, 325000, China; daijianyi2008@163.com

6. School of Health Professions, Division of Public Health, Shenandoah University, Winchester, VA 22601, USA; mgamber@su.edu

7. Wenzhou Sixth People' s Hospital, Wenzhou Central Hospital Medical Group, Wenzhou, 325000, China; xiangao368@163.com

8. The Second Affiliated Hospital of Fujian Traditional Chinese Medical University, Fuzhou 350003, China; wsun3@tulane.edu

9. Robert Stempel College of Public Health and Social Work, Florida International University, Miami, FL 33174, USA

10. Department of comprehensive medicine, Wenzhou Sixth People' s Hospital, Wenzhou Central Hospital Medical Group, Wenzhou, 325000, China; michellecai666@hotmail.com

*Correspondence:

Jing Cai，MD

Department of comprehensive medicine, Wenzhou Sixth People' s Hospital, Wenzhou Central Hospital Medical Group, Wenzhou, 325000, China; michellecai666@hotmail.com; Mail address:NO.32 Dajian Lane, Wenzhou, Zhejiang,325000,China; Telephone:86-13858842508

Wenjie Sun, PhD

The Second Affiliated Hospital of Fujian Traditional Chinese Medical University, Fuzhou 350003, China; wsun3@tulane.edu

Robert Stempel College of Public Health and Social Work, Florida International University, Miami, FL 33174, USA; Mail address: 11200 SW 8th street ACH5, Miami, FL 33199; Telephone: 305 348 4903

Xiangao Jiang，MD

Wenzhou Sixth People' s Hospital, Wenzhou Central Hospital Medical Group, Wenzhou, 325000, China; xiangao368@163.com

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Conflict of Interest

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Ethical approval

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

Abstracts

The clinical features and treatment of pulmonary tuberculosis patients with COVID-19 is unclear and understudied. Here, three pulmonary tuberculosis patients with COVID-19 infection were prospectively followed from hospital admission to discharge. We provide information and experience with treatment of pulmonary tuberculosis cases with confirmed COVID-19 infection.

Dear editor,

The World Health Organization (WHO) declared the outbreak of novel coronavirus (COVID-19) a Public Health Emergency of international on Jan 30, 2020 [1]. It is well documented that certain viral infections, such as measles, have been known to aggravate pulmonary tuberculosis (TB), 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 patients with COVID-19 are unclear and understudied. To our knowledge, the coinfection of SARS-CoV-2 and mycobacterium tuberculosis (TB) has not been reported previously. Therefore, we provide information and experience with treatment of tuberculosis cases with confirmed COVID-19 infection.

The data was derived from 139 confirmed cases, which were hospitalized in Wenzhou Sixth People's hospital from January 17, 2020, to Mar 6th, 2020. Three tuberculosis 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. Patient 1 and 2 had pulmonary tuberculosis history, and were administered quadruple antituberculosis therapy, while patient 3 had untreated tuberculosis 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 and culture of *Mycobacterium* tuberculosis, etc. The onset of their symptoms varied from dry cough, chest tightness to persistent fever. Other symptoms included chest pain, diarrhea, and dyspnea. Patient 1 and patient 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 CRP, LDH and ESR. Computed tomography scans showed all of the cases presented with multiple bilateral ground-glass opacities and consolidation, with air bronchogram.

All the patients had antivirus 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 methyl prednisolone. Since patient 3 had untreated tuberculosis 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 antivirus therapy. All of the patients recovered and were discharged from the hospital. However on the 9th 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 TB patients, 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 (OI). The CT images showed the COVID-19 lesions and tuberculosis 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* tuberculosis lesions were mainly performed as stripe of high density shadow with 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 pathology of COVID with CT imagining are warranted.

TB is the type of infection that requires cellular immunity, and nearly one hundred 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 broncholithiasis [4]. Structural changes lead to obstructive, restrictive, or mixed patterns of impaired pulmonary function. Studies in patients with pulmonary tuberculosis (PTB) have demonstrated that 33.3-94.0% of such patients develop impaired pulmonary function [5]. The risk factors for TB 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 tuberculosis[6]. This study suggests that previous lung disease such as treated or untreated mycobacterium tuberculosis (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 COVID-19 patients, 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 pulmonary tuberculosis patients with COVID-19. In this study, elderly patients with tuberculosis 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.

Authors' contributions

Dr Cai and Dr He conceptualized and designed the study, collected data, drafted the initial manuscript, reviewed and revised the manuscript.

Prof Sun conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Shi and Dr Dai collected data, and reviewed and revised the manuscript.

Dr Wu carried out the analyses, critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript.

Dr Jiang and Dr. Gamber 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.

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Figure Legend

Figure1. Axial CT images of chest in patient 3 with the COVID-19 and tuberculosis coinfection. (a) CT obtained on day 2. (a1) Stripe of high density shadow with cavitating lesion in right upper lobe. (a2) Stripe of high density shadow in right upper lobe.(a3) Pathy ground-glass opacities (GGO) in left lower lobe. (b) CT obtained on day 7.(b1) Stripe of high density shadow with cavitating lesion in right upper lobe, slight GGO in left upper lobe. (b2) Stripe of high density shadow on right middle lobe, subpleural (GGOs) in the right upper lobe. Multifocal, limited GGO is seen in the left lungs.(b3) Increased multiple ground-glass opacities and consolidation in left lower lobe with air bronchograms.(c) CT obtained on day 16. (c1) Stripe of high density shadow with cavitating lesion in right upper lobe, slight GGO in left upper lobe. (c2) Stripe of high density shadow on 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 cavitating lesion in right upper lobe, absorption of GGO in left upper lobe. (d2) Stripe of high density shadow on 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 cavitating lesion in right upper lobe. (e2) Stripe of high density shadow on right middle lobe, absorption of GGO bilaterally.(e3) absorption of GGO in left lower

lobe. Yellow arrow demonstrated the lesion of tuberculosis. Green arrow demonstrated the lesion of COVID-19.

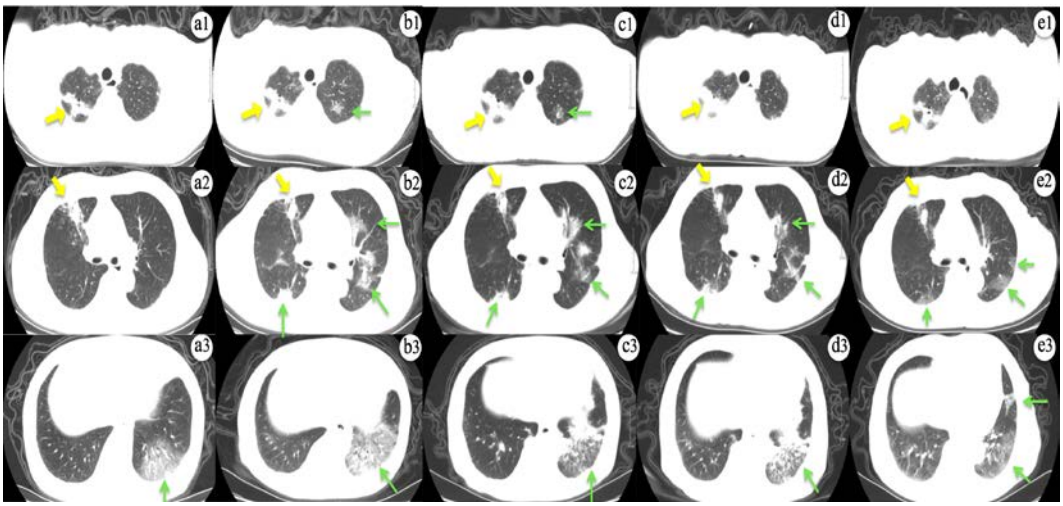

Table 1. Illustrates the clinical features, laboratory tests, clinical prognosis, treatments and outcomes of the three patients.

	Patient Number		
	1	2	3
Age (years)	67	26	76
Gender (M/F)	M	M	M
BMI	24.2	28.73	17.96
Past history	TB (Treated 6years ago) HBP	TB (treated 2 year ago)	TB (for 50 years, non-treated) Exfoliative dermatitis

			Arthrolithiasis
Smoking history	+	-	+
Imported case from Wuhan	+	+	-
Clinical features			
Fever (Tmax,℃)	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($\times 10^9$/liter)	3.3 ↓	3.2 ↓	3.9 ↓
Lowest lymphocyte count($\times 10^9$/liter)	0.5 ↓	0.8 ↓	0.3 ↓
Lowest PaO_2 (kPa)	6.7 ↓ (FiO_2 33%)	NA	9.3 ↓ (FiO2 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 thorax (Radiograph /Computed tomography)			
Initial change	Multiple bilateral mass ground-glass opacities, stripe of high density shadow on right upper lobe （Day7）	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 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 Day18 (Day 24) Unchanged image (Day35) 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	-	+	-

Treatment and outcome			
Aerosol therapy with interferonα-2b	+	+	+
Antivirus medicine	Lopinavir + Ritonavir	Lopinavir + Ritonavir	Lopinavir + Ritonavir
	Arbidol	Arbidol	Arbidol
Methyl prednisolone	+ (Day10-Day11)	-	+ (Day5-Day12)
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	Relief	Relief
	Last OI[#] 325		Last OI 396
Hospital stay (days)	37	28	24

ALT*=alanine aminotransferase. ALB[†]=albumin. CKP[‡]=creatine kinase. LDH[§]=lactic dehydrogenase. ARDS[¶]=Acute respiratory distress syndrome. OI[#] = Oxygenation Index= PaO_2/FiO_2.