Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Clinical diagnostic value of CT imaging in COVID-19 with multiple negative RT-PCR testing

Dear Editor,

At the end of December 2019, an outbreak of unexplained pneumonia in Wuhan [1,2] was caused by Severe Acute Respiratory Syndrome Coronavirus −2 (SARS-CoV-2) infection named Coronavirus Disease-19 (COVID-19). As of February 22, 2020, widespread human-to-human transmission has resulted in 76,396 cases with 2,348 deaths in 26 countries. Clinically, we have found that some patients had initial negative RT-PCR results, but chest CT had typical imaging findings, including ground-glass opacification (GGO) and/or mixed consolidation. Early detection, early diagnosis, early isolation, and early treatment of these cases can effectively control the spread of the epidemic and the emergence of large outbreaks.

A 56-year old patient who traveled to Wuhan, China 5 days ago was admitted to the emergency department for an hyperthermia (39.1 ˚C) evolving for 1 day. Laboratory studies showed white blood cell count, lymphocyte cell count and serum procalcitonin were normal.

Several additional laboratory tests were abnormal, including C-reactive protein (48.65mg/L; normal range, 0–10 mg/L), erythrocyte sedimentation rate (23 mm/h; normal range, 0–20 mm/h) and alanine aminotransferase (57 U/L; normal range, 5–40 U/L). On admission, chest CT scan revealed multiple ground-glass opacities in both lungs, especially the extrapulmonary bands and subpleural distribution (Fig. 1 A). Three RT-PCR assay of the oropharyngeal swab samples were negative for the SARS-CoV-2 nucleic acid. After antiviral (ribavirin) and symptomatic treatment, repeat chest CT showed significant progression of multi-focal ground-glass opacification and mixed consolidation that most appeared at peripheral area of both lungs (Fig. 1 B). Therefore, we performed the fourth SARS-CoV-2 nucleic acid test and the result was positive. In the end, the patient was diagnosed with COVID-19 pneumonia.

We performed RT-PCR experiments in strict accordance with the officially recommended standard protocols. Total RNA was extracted from clinical specimens with the MagNA Pure 96 system (Roche, Penzberg, Germany). RT-PCR was conducted by iCycler thermocycler (Bio-Rad Laboratories Inc., Hercules, CA) using IQSYBR Green SuperMix (Bio-Rad Laboratories Inc., Hercules, CA) and 300 pmol/mL each primer to determine the RNA expression levels of SARS-CoV-2. Primer names and sequences were provided by the Chinese Center for Disease Control. ORF1ab-F, 5′-CCCTGTGGGTTTTACACTTAA-3′; ORF1ab-R, 5′-ACGATTGTGCATCAGCTGA-3′; ORF1ab-P,5′-CCGTCTGC GGTATGTGGAAAGGTTATGG -3′. Thermal cycling was performed at 55 ˚C for 10 min for reverse transcription, followed by 95 ˚C for 3 min and then 45 cycles of 95 ˚C for 15s, 58 ˚C for 30s.

This case was finally diagnosed with COVID-19 pneumonia, and we have performed a total of 4 swab tests. The collection, transportation, storage, nucleic acid detection reagents, and nucleic acid amplification instruments of the clinical samples were performed strictly in accordance with the standards recommended by the Chinese Center for Disease Control. Therefore, the most likely cause of the positive result of the fourth swab test for SARS-CoV-2 is a considerable increase in the amount of virus, which is related to the worsening of the patient's condition. Firstly, the clinical manifestations of the patient showed significant symptoms of high fever, shortness of breath, cough, sputum, and fatigue, compared with that at admission. Secondly, bilateral coarse breath sounds with wet rales distributed at the bases of both lungs were heard on auscultation. Thirdly, repeat chest CT showed a great progression of multi-focal GGO and mixed consolidation that most appeared at peripheral area of both lungs compared to the previous chest CT. One study illustrated that the CT imaging feature of COVID-19 pneumonia is bifocal extra-zonal distribution, bilateral and multifocal [3]. Another study showed that chest CT was more sensitive than RT-PCR (98% and 71%, respectively) [4].This is consistent with the imaging findings of this case we reported.

According to current diagnostic criteria [5], etiological examinations (such as swab tests) have become the gold standard for diagnosing SARS-CoV-2 infection and removing patient isolation. However, due to the time-consuming laboratory tests and the lack of viral substances in

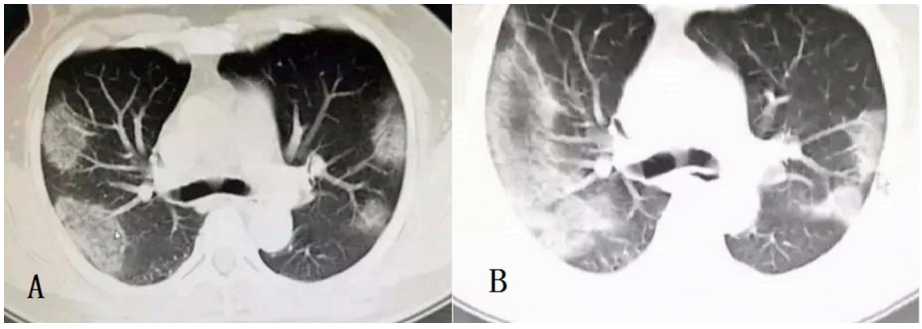

Fig. 1. Chest CT imaging of the patient.
(A) Chest CT scan revealed multiple ground-glass opacities in both lungs, especially the extrapulmonary bands and subpleural distribution.
(B) Repeat chest CT showed a great progression of multi-focal GGO and mixed consolidation that most appeared at peripheral area of both lungs.

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the samples, the RT-PCR positive rate is relatively low, so it cannot meet the needs of the growing infected population. If patients have clinical symptoms, epidemiological characteristics, and chest CT imaging characteristics of viral pneumonia that are compatible with COVID-19 infection, we need to carefully consider the isolation and treatment of these patients even if the RT-PCR test is negative.

Patient consent for publication

Obtained.

Declaration of competing interest

None declared.

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Wendong Hao*

Department of Respiratory Medicine, The Affiliated Hospital of Yan'an University, Yan'an, 716099, Shaanxi, People's Republic of China

Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, 710061, Shaanxi province, People's Republic of China

E-mail address: hwdokgood@hotmail.com.

Manxiang Li

Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, 710061, Shaanxi province, People's Republic of China

* Corresponding author.