CT features of COVID-19 patients with two consecutive negative RT-PCR tests after treatment

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Abstract

Purpose: The objective of this study is to expound the CT features of COVID-19 patients whose nucleic acid tests converted to negative after treatment.

Materials and Methods: We retrospectively reviewed 46 COVID-19 patients with two consecutive negative RT-PCR tests after treatment. The cases were divided into moderate group and severe/critical group according to disease severity. Clinical and CT scanning data were collected. CT signs of pulmonary lesions and the score of long involvement were expounded.

Results: 39 moderate cases and 7 severe/critical cases were included. All moderate patients showed peripheral lesions while severe/critical cases exhibited both central and peripheral lesions with all lobes involvement. Ground glass opacity (GGO) and mixed GGO were observed. Aberrant pulmonary interstitium manifested as reticular and thin linear pattern. Thickened blood vessels and pleural thickening were found. Pulmonary fibrosis, annular thickening of the bronchial wall, bronchiectasis, air bronchogram and small amount of bilateral pleural effusion were observed in severe/critical patients. The severe/critical group showed higher CT score of involvement.

Conclusions: Pulmonary lesions persisted even after twice consecutive nucleic acid tests converted to negative. We strongly recommended regular follow-up of CT scans after nucleic acid tests conversion. Evaluation of complete remission should base on chest CT.

Introduction

Coronavirus Disease-2019 (COVID-19) is an acute infectious disease mainly involving the respiratory system [1]. The highly contagious disease is caused by a novel coronavirus currently termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. So far to April 9, 2020, 1479748 cases of COVID-19 patients and 87444 deaths are reported. It is a huge strike to human health and draws much attention from countries all over the world.

At present, etiological examinations, including reverse transcription-polymerase chain reaction (RT-PCR) and gene sequencing of sputum, throat swab and lower respiratory tract secretion, are the gold standard for diagnosis of COVID-19[2], and are served as the primary criteria of discharge after treatment. However, it remains unclear whether damage to the lung have been completely restored when the nucleic acid tests convert to negative after treatment. Explanation of this issue is essential for determining the timing of treatment termination and isolation release.

Chest computed tomography (CT) provides us a powerful noninvasive mean for the diagnosis and monitoring for COVID-19. Ground glass opacity (GGO) and consolidative opacity involving bilateral and peripheral lung were CT hallmarks of COVID-19 pneumonia [3-8]. It has been reported that CT manifestations vary depending on the infection time course [8]. However, post-treatment patterns of CT images after nucleic acid tests conversion have not yet been described, which are paramount for not only understanding the pathophysiology but also developing management strategies. In the present study, we assessed chest CT images of COVID- 19 patients whose nucleic acid tests converted to negative after treatment, aimed to provide the most up to date evidence and recommendations for the evaluation of COVID-19 remission.

Results

Clinical Characteristics

In the study, 39 cases including 17 men and 22 women were included in moderate group. Age of moderate cases ranged between 22 to 68 years, with an average of 46.2±13.3 years. Twenty-three moderate patients(59%) presented with clinical symptom: 4 (10%) had fever, 5 (13%) had cough without sputum, 6 (15%) coughed with sputum, 2 (5%) felt chest tightness, 4 (10%) had polypnea, 2 (5%) had fatigue, 2 (5%) had diarrhea, 2 (5%) had throat discomfort.

Seven cases including 2 men and 5 women were divided into severe group. Age of severe cases ranged between 33 to 85 years with an average of 57.8±15.8 years. Three patients (43%) had no obvious clinical symptom, 1 patient (14%) had fever, 2 patients (29%) coughed without sputum, 1 patient (14%) coughed with sputum. Demographic and clinical characteristics were presented in table 1.

CT Findings

CT features of COVID-19 patients with two consecutive negative RT-PCR tests after treatment were presented in Figure 1 and summarized in table 2. Among 39 moderate patients, 3 (8%) had single lesion while 36 (92%) showed multiple lesions. All moderate patients had visible lung peripheral lesions while 6(15%) of them had lung central lesion simultaneously. Nine moderate patients (23%) showed single lung lobe involvement, 13 (33%) showed two to four lung lobes involvement, and the rest (44%) showed all lung lobes involved. Lesion pattern was circular, fan-shaped, pulmonary fibrosis and irregular in 18 (46%), 19 (49%), 22 (56%) and 34 (87%) moderate cases, respectively. Density features manifested as GGO in all, mixed GGO in 16 (41%) and consolidation in 4 (10%) moderate cases. Twenty-eight moderate patients (72%) had pulmonary interstitium thickening, of whom 5(13%) had only linear interstitial thickening while 23 cases (59%) suffered both linear and reticular interstitial thickening. Besides, blood vessel thickening, bronchial wall thickening, bronchiectasis and air bronchogram were observed in 30 (77%), 1 (3%), 3 (8%) and 5 (13%) moderate patients. Bilateral pleural effusion was noted in 1 patient (3%). Pleural thickening was found in 19 moderate patients (49%), and 12(31%) of them showed pleural adhesion. Results for the score of lungs showed among moderate cases, 29 (74%) were 0-5 points, 8 (21%) were 6-10 points and 2 (5%) were 16-20 points.

With regard to the 7 severe patients, all showed multiple lesions with all lobes involvement, of whom 2 (29%) presented with peripheral lesions while 5 (71%) showed both central and peripheral lung involvement. All severe cases had fan-shaped and irregular-shaped lesions, and 5 (71%) showed pulmonary fibrosis. All severe cases manifested as visible GGO and mixed GGO, of whom 5 (71%) had consolidation simultaneously and 4 (57%) showed air bronchogram. All severe cases showed pulmonary interstitium thickening in form of linear thickening, 6 (86%) of them exhibited reticular thickening additionally. Blood vessels thickening were observed in all severe cases. Bronchiectasis was observed in 3 severe cases (43%), and 2 (29%) of them showed annular thickening of the bronchial wall. Six severe cases (86%) presented with pleural thickening, and 5 (71%) of them showed pleural adhesions simultaneously, besides, small amount of bilateral pleural effusion was found in 3 (43%) of these 5 cases. Scores of lungs were calculated based on lesion involvement range: 2 severe patients (29%) were between 6 to 10 points, 1 (14%) was between 11 to 15 points and 4 (57%) were between 16 to 20 points.

Discussion

According to current criteria for end-of-treatment outcomes among COVID-19 patients, etiological examinations, such as swab RT-PCR tests, have become the gold standard for clinical cure and removing patient isolation. However, our study demonstrated that the pulmonary lesions persisted even after RT-PCR conversion. Multiple lesions such as GGO, pulmonary interstitium thickening, pleural effusion remained prevalent when nucleic acid tests converted to negative, indicating the presence of non-parallel relationship between SARS-CoV-2 nucleic acid tests and chest CT abnormalities.

Among all 46 patients, multiple lesions were noted in CT images, with multiple lung lobes involved. Common type patients mainly showed lung peripheral lesions, while severe type patients exhibited both peripheral and central lesions. This was similar with the statement of other earlier COVID-19 reports [5-7, 9-11]. The main pattern of lesions was irregular in this study while circular or fan-shaped in early stage of the disease, which is a differentiation [5, 12]. It is probably related to the natural progress of COVID-19. Irregular signs maybe caused by unsynchronized lesion absorption and inter-fusion. In addition, we observed the pulmonary fibrosis from 5 intensive patients, which caused by lesion absorption and recovering.

GGO remained the most common finding after nucleic acid test converted to negative. Different from the earlier state, mixed GGO and consolidation was dominant after treatment [9]. What we have to point out is that air bronchogram can be found in consolidation lesion and some patients had visible bronchial wall thickening and bronchiectasis, which showed inflammation in the bronchi of the lungs.

Pulmonary interstitium thickening is another important sign of COVID-19 pneumonia, which showed more apparent in CT images after nucleic acid tests conversion. Pulmonary interstitium thickening became reticular pattern, in contrast it was mainly linear thickening in earlier stage. Pleural thickening and pleural adhesion in COVID-19 patients were rarely reported to date [6, 10]. However, visible pleural thickening was observed in half of the common type patients, of whom a majority presented with pleural adhesion simultaneously. Furthermore, pleural thickening and pleural adhesion were even more common in severe cases. In addition, small amount of bilateral pleural effusion was observed from 1 common type patient and 3 severe type patients. The pleural abnormalities indicated pleural inflammation were encountered in COVID-19 patients, especially in severe cases.

The lung scoring method in this study is able to reflect the approximate range of COVID-19 pneumonia. The score of common type patients were mostly (29 of 39 patients) between 0 to 5 points, while the score of severe type patients were mostly (4 of 5 patients) between 16 to 20 points. From the point of lesion involvement range, severe type patients' lesion range was much wider than that of common type patients even though their nucleic acid test results turned negative.

In clinical practice, two consecutive negative nucleic acid tests were regarded as the most important basis for discharge, however, it should be interpreted with caution, since, in our study, two consecutive negative RT-PCR tests did not signify complete cure of COVID-19 pneumonia. Even though antiviral treatment resulted in progressively lower levels of SARS-CoV-2 until the virus is no longer detectable, the tissue damage caused by overexuberant inflammatory response [13] was far from complete restoring, instead, aggravation coexists with recovery, as observed in the CT images.

Although we cannot exclude the possibility that laboratorial error could have contributed to some of the inconsistency between nucleic acid tests and chest CT manifestations, the patterns of CT lesions observed in this study suggest that the bulk of the discrepant results reflected the persistence of pulmonary damage despite negative nucleic acid tests. Based upon these results, we would specifically discourage the use of nucleic acid tests results alone for treatment discontinuation and quarantine release decisions, while regular chest CT scans were strongly recommended even after nucleic acid tests conversion to monitor post-treatment cure.

There are some limitations in this study. Firstly, the time from negative nucleic test to CT scanning was not exactly the same, as CT reexaminations were carried out at different time of intervals according to each patient's condition, which was longer for moderated cases and shorter for severe cases. Secondly, we had not performed further investigation of the pulmonary lesions, due to the lack of inspection equipment in temporary isolation wards. Bronchoscopy, bronchoalveolar lavage and lung biopsy are required to further confirm the nature of the lesions.

In conclusion, residual pulmonary lesions remained significant after nucleic acid tests convert to negative, and became more sophisticated and diverse in comparison with that in earlier stage. These findings provided important insights for pathological mechanism and therapeutic efficacy evaluation of COVID-19, suggesting that chest CT was better than nucleic acid conversion in assessing the final treatment outcomes of the patients. Our results highlighted the importance of using both chest CT and nucleic acid test rather than nucleic acid test alone for monitoring of COVID-19 patients. Evaluation of complete remission should base on chest CT.

Materials And Methods

Ethical approval

The ethics committee of The People's Hospital of Guangxi Zhuang Autonomous Region approved this retrospective study and waived the requirement for informed consent. This study was conducted in compliance with the Declaration of Helsinki.

Study Population

In this retrospective study, 46 COVID-19 patients treated in the People's Hospital of Guangxi Zhuang Autonomous Region from February 16, 2020 to March 8, 2020 were included. Patients had no abnormal manifestations on CT throughout the disease course were excluded. All patients underwent two consecutive nucleic acid tests (obtained at least 24 hours apart) and the results showed negative. Chest CT was performed right after the two negative nucleic acid tests and the images were reviewed.

The patients were grouped based on the illness severity defined by the National Health Commission of China [14]. The severe cases met at least one of the following :1) breathing rate ≥30 breaths per minute; 2) pulse oximeter oxygen saturation ≤93% in a resting state; 3) arteria oxygen tension /inspiratory oxygen fraction ≤300 mmHg; 4) respiratory failure (arteria oxygen tension<60 mmHg when breathing ambient air) occurred and mechanical ventilation required; 5) hemodynamic shock; 6) patients with other organ failure needed intensive care unit monitoring and treatment. Mild patients without CT findings throughout the disease course were not included in the study, so the rest cases were divided in moderate group.

CT Scanning Protocol

CT examinations were performed on a 64-detector row SOMATOM go. Top (Siemens Healthineers, Germany) with the following parameters: tube voltage: 120 kVp, tube current with the automatic milliampere technology: 32–200 mAs, pitch: 1.5, tube rotation time: 0.5 s, matrix: 512×512, slice thickness: 0.6 mm, reconstruction thickness: 1.0 mm. Unenhanced CT scans were obtained for all patients. Patients were scanned in the supine position, during breath hold. Three chest radiologists with 7 years of experience in thoracic radiology retrospectively reviewed the images independently, with a final finding reached by consensus when there was a discrepancy. The score of lungs was calculated based on the range of lesion involvement: 1%-25% involvement is scored as 1 point, 26%-50% as 2 points, 51%-75% as 3 points and 76%-100% as 4 points. Each lung lobe is assessed and then total scores are calculated.

Statistical Analysis

All statistical analyses were performed with the SPSS 17.0 software package (SPSS Inc, Chicago, IL, United States). Continuous normally distributed variables were presented as the means ± SD. Categorical variables were presented as frequencies or percentages.

Declarations

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Author contributions

Y. Wei, Lu, K. Ye, H. Liu collected the clinical and CT imaging dataset.

Z. Fu, Chen, Y. Yang processed and analyzed the data. Y. Yang provided statistical analysis. Z. Fu, F. Xu, L. Ma conceived the project. Z. Fu, N. Tang, F. Tang, G. Huang edited the paper.

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Declaration of interests

All authors declare no competing interests.

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Tables

Table 1: Demographic and clinical characteristics of COVID-19 patients with two consecutive negative RT-PCR tests after treatment

Characteristic	Common type n=39	Severe type n=7
Age（years）	46.2±13.3	57.8±15.8
Gender(man)	17 (44%)	2(29%)
Days from nucleic acid test result indicates negative to CT Scan	2.7	1.7
Symptoms		
Fever	4(10%)	1(14%)
Dry cough	5(13%)	2(29%)
expectoration	6(15%)	1(14%)
Chest tightness	2(5%)	0(0%)
Polypnea	4(10%)	0(0%)
Fatigue	2(5%)	0(0%)
Diarrhea	2(5%)	0(0%)
Throat discomfort	2(5%)	0(0%)

Table 2: CT features of COVID-19 patients with two consecutive negative RT-PCR tests after treatment

Feature	moderate n=39	Severe/critical n=7
Number		
Unique	3 (8%)	0(%)
Multiple	36(92%)	7(100%)
Distribution		
Peripheral	33(85%)	2(29%)
Peripheral involving central	6(15%)	5(71%)
Density		
Ground glass opacity	38(97%)	7(100%)
Mixed ground glass opacity	16(41%)	7(100%)
Consolidation	4(10%)	4(57%)
Lobes involved		
Single lobe	9(23%)	0(0%)
2~4 lobes	13(33%)	0(0%)
5 lobes	17(44%)	7(100%)
Shape		
Circular	18(46%)	3(43%)
Fan-shaped	19(49%)	7(100%)
Irregular	34(87%)	7(100%))
Pulmonary fibrosis	22(56%)	5(71%)
Pulmonary interstitium thickening	28(72%)	7(100%)
Only linear	5(13%)	1(14%)
Linear + reticulation	23(59%)	6(86%)
Other findings		
Air bronchogram	1(3%)	4(57%)
Vascular enlargement	30(77%)	7(100%)
Bronchial wall thickening	3(8%)	2(29%)
Bronchiectasis	5(13%)	3(43%)
Pleural thickening	19(49%)	6(86%)
Pleural adhesion	12(31%)	5(71%)
Pleural effusion	1(3%)	3(43%)
Total CT score		
0~5	29(74%)	0(0%)
6~10	8(21%)	2(29%)
11~15	0(%)	1(14%)
16~20	2(5%)	4(57%)

Figures

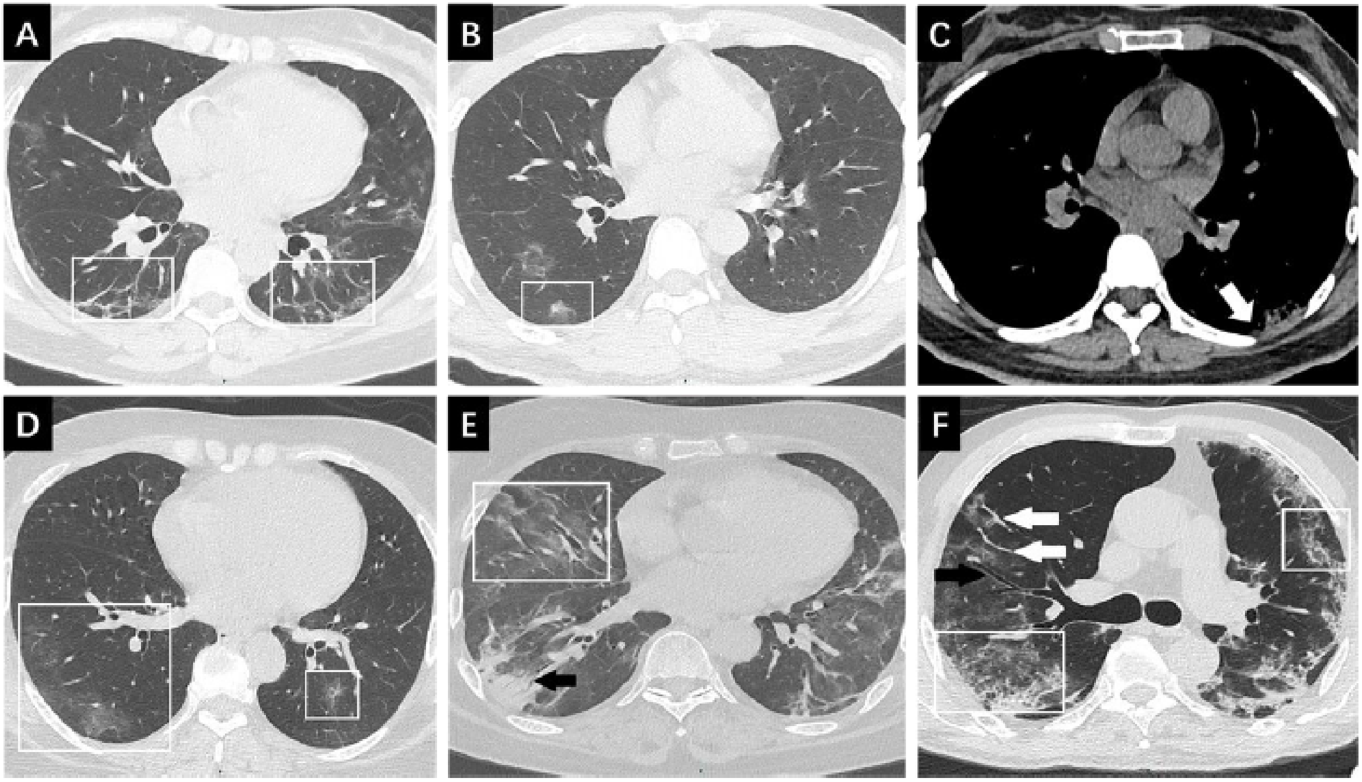

Figure 1

CT images of patients with COVID-19. A 56-year-old woman with moderate COVID-19. CT image shows pulmonary fibrosis in both lungs (box). B 37-year-old man with moderate COVID-19. CT image shows mixed ground glass opacity (box). C 32-year-old woman with moderate COVID-19. CT image shows pleural thickening with pleural adhesion (arrow). D 50-year-old woman with severe COVID-19. CT image shows ground glass opacities in both lungs (box). E 59-year-old woman with severe COVID-19. CT image shows ground glass opacities (box) and consolidation with air bronchogram (arrow) in the right lung. F 65-year-old man with severe COVID-19. CT image shows bronchial wall thickening and bronchiectasis (black arrow). Vascular enlargement is also shown (white arrows). The two boxes show pulmonary interstitium reticular thickening in both lungs.