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Thin-Section Computed Tomography Manifestations During Convalescence and Long-Term Follow-Up of Patients with Severe Acute Respiratory Syndrome (SARS)

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: SARS is not only an acute disease, but also leads to long-term impaired lung diffusing capacity in some survivors. However, there is a paucity of data regarding long-term CT findings in survivors after SARS. The aim of this study was to assess the changes in lung function and lung thin-section computed tomography (CT) features in patients recovering from severe acute respiratory syndrome (SARS), especially the dynamic changes in ground-glass opacity (GGO).

Material/Methods: Clinical and radiological data from 11 patients with SARS were collected. The serial follow-up thin-section CTs were evaluated at 3, 6, and 84 months after SARS presentation. The distribution and predominant thin-section CT findings of lesions were evaluated.

Results: The extent of the lesions on the CT scans of the 11 patients decreased at 6 and 84 months compared to 3 months. The number of segments involved on 84-month follow-up CTs was less than those at 6 months ($P<0.05$). The predominant thin-section CT manifestation at 84 months (intralobular and interlobular septal thickening) was different than that at 6 months, at which GGO was predominant.

Conclusions: During convalescence after SARS, GGO and intralobular and interlobular septal thickening were the main thin-section CT manifestation. Intralobular and interlobular septal thickening predominated over GGO at 84 months.

MeSH Keywords: Pneumonia, Viral • Severe Acute Respiratory Syndrome • Tomography Scanners, X-Ray Computed

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Background

Severe acute respiratory syndrome (SARS) is an emergent infectious disease that was epidemic in 2002 and 2003 [1]. Between November 2002 and July 2003, an outbreak of SARS in southern China infected about 8000 people and led to 774 recorded deaths, mostly in Hong Kong [1]. Within weeks, SARS spread from Hong Kong to 37 countries [2]. A novel coronavirus (SARS-CoV) is responsible for SARS. The coronavirus responsible for Middle East Respiratory Syndrome (MERS-CoV) is similar to SARS-CoV. A better understanding of the features of SARS-CoV would help to guide control measures and treatment for similar diseases, such as MERS-CoV [3,4].

Lung injury caused by SARS-CoV is one of the main clinical manifestations and directly affects prognosis. Imaging plays an important role in the diagnosis and evaluation of patients with SARS. Thin-section computed tomography (CT) can show pulmonary abnormalities in patients with normal findings on plain X-ray and is useful in depicting the patterns and extent of the abnormalities [5–8]. During the acute phase of SARS, the more distinctive radiographic features include the predominant involvement of lung periphery and lower zone, and the absence of cavitation, hilar lymphadenopathy, and pleural effusion [9,10]. Radiographic progression from unilateral focal lesion to either multifocal or bilateral involvement during the second phase of the disease, followed by radiographic improvement with treatment, are commonly observed [9,10].

SARS is not only an acute disease, but also leads to long-term impaired lung diffusing capacity in about 24% of survivors [11], resulting in significantly lower exercise tolerance compared with the age-matched general population [11–13]. Another study suggested that the lung function impairment might not be related to the disease itself, but rather to extrapulmonary muscle weakness [14]. Nevertheless, 75% of SARS survivors still show lung abnormalities on thin-section CT 5 years after their illness onset [14].

However, there is a paucity of data regarding long-term CT findings in survivors after SARS. Therefore, the aim of the present study was to assess the changes in lung function and lung thin-section CT features in patients recovering from SARS, especially the dynamic changes in ground-glass opacity (GGO).

Material and Methods

Patients

Eleven patients who had been discharged after treatment for SARS as inpatients between February and June 2003 at Beijing Friendship Hospital were followed up at 3, 6, and 84 months using thin-section CT and were included in the present study. The diagnosis of SARS was based on the World Health Organization criteria [15].

This study received Ethics Committee approval from Beijing Friendship Hospital affiliated to Capital Medical University (Approval ID: 2015-P2-076-01). The committees waived the need for individual consent because of the retrospective nature of the study.

CT scans

The CT examinations were performed with an 8-row multidetector CT scanner (High Speed Ultra; GE Medical Systems, Milwaukee, WI, USA), and a 64-row multidetector CT scanner (LightSpeed Ultra; GE Medical Systems, Milwaukee, WI, USA) using the following parameters: 120 kVp, 150 mA, 5-mm collimation, 1.35:1 pitch, and reconstruction matrix of 512×512. The subjects were scanned in a supine position during breath-holding at full inspiration. Thin-section CT images were reconstructed with 0.625-mm or 1.25-mm collimation with a high spatial frequency algorithm or standard algorithm and then sent to the workstation (ADW 4.2; GE Medical Systems, Milwaukee, WI, USA) for analyzing. Thin-section CT images were evaluated using a lung window, with a window level of –600 HU and window width of 1500 HU. The soft-tissue window was not evaluated.

Image interpretation

All thin-section CT images were reviewed by 2 radiologists. The radiologists were aware of the diagnosis of SARS. For all scans, the radiologists were blinded to the names of the patients and the length of time since onset, but they were aware of which images belonged to the same patient. A consensus had to be reached between the 2 radiologists about the abnormalities. Discrepancies were solved by discussion.

The radiologists determined the extent of the following thin-section CT abnormalities: ground-glass opacity, consolidation, reticular pattern, patchy decreased attenuation, and subpleural line, in accordance with the standard morphologic descriptors based on the Fleischner Society Nomenclature Committee recommendations [16] and other studies [17,18]. The evaluation of the extent of lung involvement was based on the segments of the lung anatomy: 10 segments in the right lung and 10 segments in the left lung (2 segments were considered in the apicoposterius segment left upper lobe and 2 segments were considered in the inferior front segment of the left lower lobe). The following rules were used to evaluate the lobe involvement: if more than half of the segment on the biggest scope of lesion level on axial thin-section CT was involved, then the segment (1 point) was recorded as being involved;

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Table 1. Characteristics of the patients.

Case number	Gender	Age at onset	3 months		6 months		84 months		
			Predominant HRCT findings	Segments involved	Predominant HRCT findings	Segments involved	Predominant HRCT findings	Segments involved	PFT
1	F	30	GGO	15	Reticulation and interlobular thickening	15	Reticulation and interlobular thickening	15	Mild
2	M	35	GGO	3	GGO	2	GGO	1	Mild
3	M	54	Consolidation and GGO	8	GGO	6	Reticulation and interlobular thickening	4	N
4	F	38	Diffuse GGO	9	GGO	3	Reticulation and interlobular thickening	3	Mild
5	F	42	Consolidation and GGO	13	Reticulation and interlobular thickening	7	Reticulation and interlobular thickening	5	Mild
6	F	32	–	–	GGO	14	Reticulation and interlobular thickening	11.5	Mild
7	M	31	–	–	GGO	18	Reticulation and interlobular thickening	9.5	Mild
8	F	31	–	–	Reticulation and interlobular thickening	5	Reticulation and interlobular thickening	3.5	Mild
9	F	40	–	–	GGO	9	Reticulation and interlobular thickening	6.5	Moderate
10	F	48	–	–	GGO	18	GGO	16	Mild
11	F	36	–	–	GGO	9	Normal	0	N

if no more than half of the segment was involved, then 0.5 point was recorded.

To evaluate the distribution of the lesion, it was also classified into 3 categories: 1) subpleural and/or peribronchovascular, 2) diffuse, or 3) irregular. In addition, each CT was divided into 3 categories: 1) anterior, 2) posterior, or 3) anterior and posterior. Finally, for every CT scan, the radiologists were required to generalize the main CT manifestation: 1) GGO predominant, or 2) fine reticulation predominant.

Pulmonary function test (PFT)

The PFT of the patients was classified into mild, moderate, or serious. We evaluated lung volumes (total lung capacity [TLC], vital capacity [VC], residual volume [RV], functional residual capacity [FRC] using the nitrogen washout method), spirometry (forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1], FEV1/FVC ratio), and surface area for gas exchange (diffusion capacity adjusted for hemoglobin [DLCO]). The DLCO was determined using the single-breath carbon monoxide technique and an infrared analyzer. FEV1/expected% of <30%, 30–50%, 50–80%, and >80% were regarded as extremely serious, serious, moderate, and mild, respectively. DLCO values <80% of predicted were regarded as being impaired.

Statistical analysis

Descriptive statistics are presented. Continuous data are presented as means ± standard deviation (SD). Categorical data are presented as frequencies. SPSS 16.0 (IBM, Armonk, NY, USA) was used for statistical analysis.

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Table 2. CT findings during follow-up.

CT findings	3 months (n=5)		6 months (n=11)		84 months (n=11)	
GGO	5	(100.0%)	11	(100.0%)	10	(90.9%)
Consolidation	5	(100.0%)	0		0	
Reticulation	5	(100.0%)	9	(81.7%)	10	(90.9%)
Subpleural line	1	(20.0%)	1	(9.1%)	1	(9.1%)
Traction brochiectasis	0		2	(18.2%)	2	(18.2%)
Air trapping	1	(20.0%)	1	(9.1%)	1	(9.1%)
Small nodule	2	(40.0%)	2	(18.2%)	2	(9.1%)
GGO predominance	5	(100.0%)			2	(18.2%)
Reticulation predominance	0		3	(27.3%)	8	(72.7%)
Distribution of peripheral	3	(60.0%)	9	(81.7%)	9	(81.7%)
Distribution on axial section (anterior and posterior)	5	(100.0%)	11	(100.0%)	10	(90.9%)
Segments involved	48	(48/500)	106	(106/2200)	75	(75/2200)

Results

Characteristics of the patients

Eleven patients (8 females and 3 males; age range: 30–54 years, mean age: 38.6 years) met the selection criteria. Table 1 presents the demographic data and changes in lung function and lung radiographic features of the 11 patients during follow-up. All of the 11 patients were healthy before developing SARS and none were smokers. In acute phase, glucocorticoid was used in all 11 patients (methylprednisolone; the biggest dose was 840 mg/d, mean duration 9.5 days, and after improving for 2 or 3 days, methylprednisolone dose was decreased). All patients were still alive during the study period. Twenty-seven CT scans were evaluated. At 84 months, 5 patients were still experiencing persistent dyspnea, 4 had cough, 2 had sputum production, and 2 experienced all 3 symptoms. The mean time from discharge to the first follow-up was 3 months (range, 2 to 4 months).

Thin-section CT findings

Table 2 presents the thin-section CT findings. All 11 patients underwent CT scans at 6- and 84-month follow-up. Multiple lobes or segments were involved in all 11 cases. Among them, 48 segments (average of 10 segments per patient) were involved at 3 months, 106 segments (average of 9.6 per case) were involved at 6 months, and 75 segments (average of 6.8 per case) were involved at 84 months. At 3 months, as the predominant thin-section CT feature, 2 patients (40.0%) showed GGO (Figure 1) and 3 showed consolidation and GGO (60.0%) (Figure 2). At 6 months, as the predominant thin-section CT feature, 3 patients (27.3%) showed reticulation and interlobular thickening (Figure 3) and 8 (72.7%) showed GGO. At 84 months, as the predominant thin-section CT feature, 1 patient (9.1%) had no lung abnormality, 8 patients (72.7%) showed reticulation and interlobular thickening, and 2 (18.2%) showed GGO. Traction bronchiectasis was found in 3 patients (Figure 3), while patchy decreased attenuation was found in 1 patient (Figure 1). Traction bronchiectasis was found at 6- and 84-month thin-section CT, and patchy decreased attenuation was found at 3-, 6-, and 84-month thin-section CT.

Pulmonary function test

The PFT results of the 11 patients at 84 months are presented in Table 1. Two patients (18%) had a normal PFT. Nine patients (81.8%) had a low DLCO. Eight patients (72.7%) had mild lung function damage, and 1 (9.1%) had moderate lung function damage.

Trends in changes in predominant thin-section CT findings over time

Table 2 shows that the predominant CT findings in SARS survivors shift from a predominance of the GGO feature at 3 (100.0%) and 6 (72.7%) months to the predominance of reticulation and interlobular thickening at 84 months (72.7%). Figuress 1–3 present typical thin-section CT imaging at 3, 6, and 84 months, respectively.

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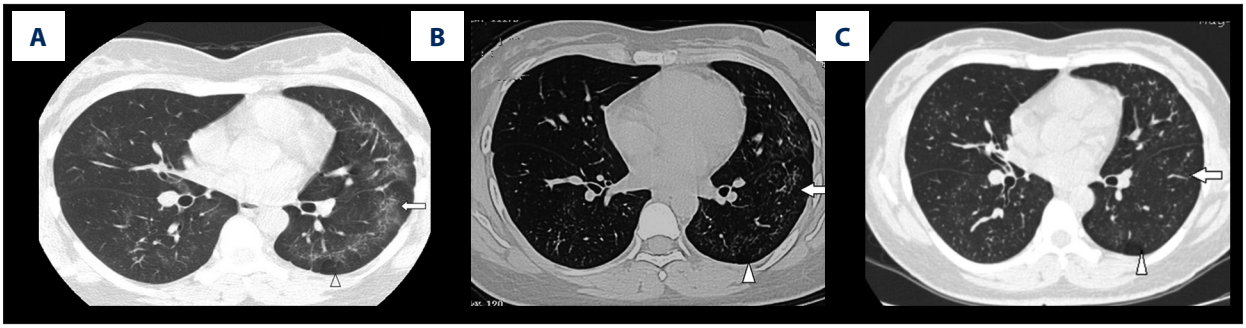

Figure 1. Case 1, SARS survivor, female, 30 years old. (**A**) The CT scan at 3 months showed diffuse bilateral GGO (arrow). (**B**) Six months later, GGO was reduced. (**C**) At 84 months, GGO was greatly reduced and fine reticulation (intralobular and interlobular septal thickening) predominated (arrow). Patchy decreased attenuation was seen at 3-, 6-, and 84-month CT (triangle).

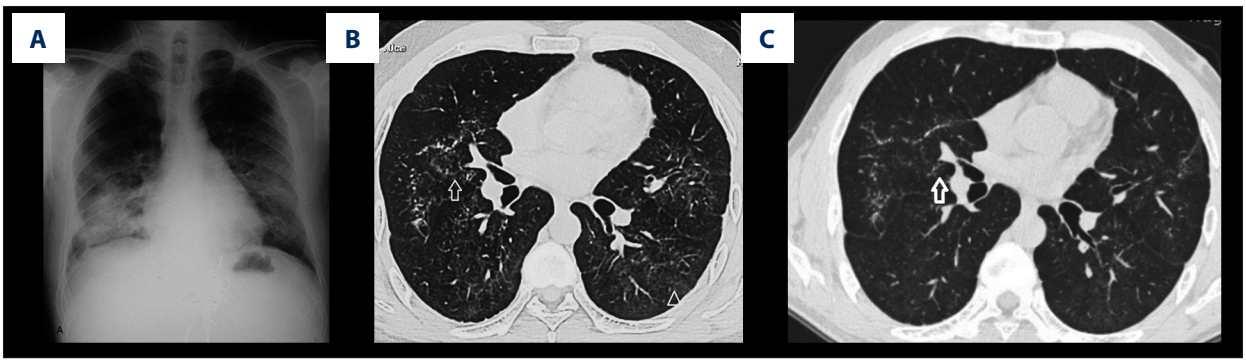

Figure 2. Case 7, SARS survivor, male, 31 years old. (**A**) Chest radiography showed consolidation in the lower lobes of both lungs in acute phase. (**B**) Six months later, GGO (triangle) and reticulation (arrow) were observed in both lungs. (**C**) Fine reticulation (arrow) still persisted but GGO could not be found at 84-month CT.

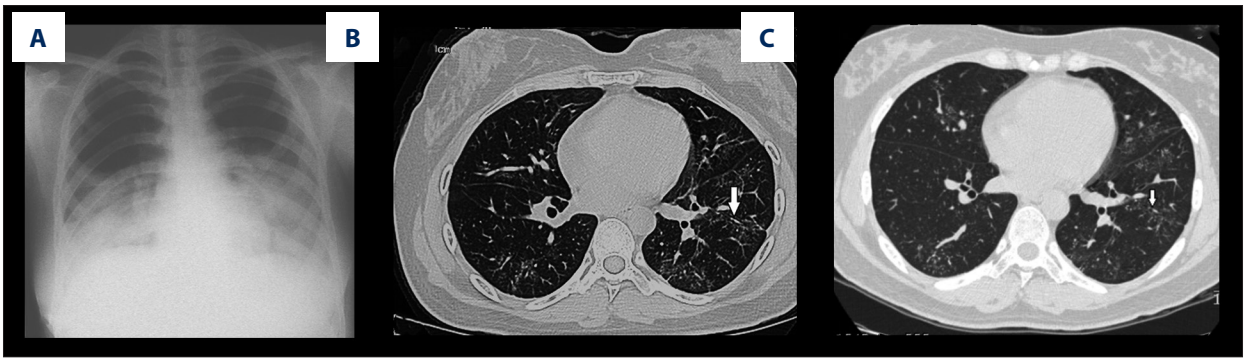

Figure 3. Case 6, SARS survivor, female, 32 years old. (**A**) X-ray radiography showed a large consolidation in the lower lobes of both lungs in acute phase. (**B**) Six months later, X-ray revealed GGO, septal thickening, and fine-mesh shadows (white arrow). Traction bronchiectasis was found in the left lower lobe. (**C**) At 84 months, GGO was reduced and interlobular thickening predominated. Traction bronchiectasis was still present.

Discussion

During viral lung infections, the lungs histologically show diffuse alveolar damage, including interstitial lymphocyte infiltration, air-space hemorrhage, edema, fibrosis, type 2 cell hyperplasia, and hyaline tissue formation [19]. Diffuse alveolar damage is found in some kinds of viral pneumonia, but it is usually self-limited and radiologic abnormalities usually diminish within 3 weeks in immunocompetent patients [20]. In SARS-CoV-infected patients, intralobular and interlobular septal thickening, subpleural lines, and traction bronchiectasis were observed as late as 84 months after SARS infection in the present study. All these thin-section CT manifestations were also found at 3 and 6 months during the recovery phase

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of SARS, which may indicate lung fibrosis, as observed in previous studies [21,22]. To the best of our knowledge, the present study is the first to report abnormal imaging at up to 7 years after SARS-CoV pneumonia.

The characteristic thin-section CT finding in SARS survivors changed from GGO predominance at 3–6 months to fine reticulation (intralobular and interlobular septal thickening) predominance at 7 years. GGO was found in 8 patients at 6 months and in 2 patients at 84 months. Some studies reported the imaging features of the recovery phase in patients with SARS [21,22]. Antonio et al. [21] analyzed the thin-section CT findings at an average of 36.5 days in 24 patients and observed that the main findings in the recovery phase were GGO, intralobular and interlobular septal thickening, traction bronchiectasis, and subpleural lines. They also reported that fibrosis began early and tended to be found in elderly and more seriously affected patients. However, in the present study, all 11 patients showed abnormalities that may indicate fibrosis at 6 months, and 10 patients still had signs of lung fibrosis after 7 years. All patients were 30–54 years old when they were infected by SARS-CoV; therefore, lung fibrosis could be a long-term sequela of SARS-CoV infection.

Importantly, the thin-section CT lung abnormalities observed in the present study seemed to be different from those induced by other pneumonia viruses [23,24]. It is known that many SARS patients suffer from ARDS/DAD in the acute phase [25]. Nevertheless, the present study suggests that either the lung fibrosis is very slow to disappear after infection or that the CT abnormality is different from lung fibrosis induced by other pneumonia viruses. However, the results of the present study do not resolve this issue. With regard to the physical impairment that may accompany the abnormalities on thin-section CT, some previous studies suggest that the physical impairment after SARS persists for at least 12 months [11,13], while another study suggests only mild impairments at 5 years [14]. A study has shown that the immune response after SARS persists for at least 90 days [26], but no data is available to determine exactly how long it persists and whether it could involve lungs as a long-term sequela. In our study, mild or moderate pulmonary function damage was still present in 81.8% of the patients at 7 years after SARS infection.

Some studies have shown that after the acute phase of ARDS, CT findings are variable [26–28]. In ARDS, although complete resolution of abnormalities may occur, the typical CT findings at the later stage are that of a coarse reticular pattern and GGO in the anterior part of the lungs [25,27,29]. In this setting, it is likely that GGO represents areas of fine fibrosis, which are observed on thin-section CT. Our study shows that the CT abnormalities of all patients had a diffuse distribution, which was similar that reported in a recent study by Masclans et al. [30]. Indeed, Masclans et al. [30] found that 76% of patients had abnormalities on high-resolution CT at 6 months after infection, and these abnormalities were typically areas of reticulation and GGO. Therefore, the distribution of thin-section abnormalities in our study seem to be different from those reported in some other studies [25,27,29] on late-stage ARDS. However, drawing conclusions is impossible because of the lack of accompanying histopathological examination in most patients with SARS and ARDS.

Another finding of the present study is the presence of traction bronchiectasis, which represents airway abnormalities, as well as patchy decreased attenuation, which probably represents airway abnormalities. Traction bronchiectasis was found in 3 patients, while patchy decreased attenuation was found in 1 patient. Similar results in SARS patients were also reported in some other studies [24,31]. Masclans et al. [30] found that airway disease was more common in ARDS survivors, again suggesting the possibility of the presence of underlying lung fibrosis in these survivors of SARS.

The present study is not without limitations. This was a retrospective review of patients evaluated at 2 centers, with all of the issues of selection and observational biases that this design entails. Secondly, the sample size was smaller than that of prior studies and may not represent most patients. Thirdly, the pulmonary function test results at 3 and 6 months were unavailable in most patients.

Conclusions

This study of 11 SARS patients found that lung abnormalities on thin-section CT still existed in SARS survivors 7 years after infection, though the extent became less. During convalescence after SARS, GGO and intralobular and interlobular septal thickening were the main thin-section CT manifestations. From 6 months to 7 years after SARS, the predominant thin-section CT findings changed from GGO predominance to fine reticulation predominance, which probably represents the interstitial fibrotic proliferation recovery phase of diffuse alveolar damage. These abnormalities were consistent with the PFT.

Conflict of interest

The authors declare that they have no actual or potential conflicts of interest.

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