Chapter 8

The Role of Imaging in the Follow up of SARS

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Introduction

Severe Acute Respiratory Syndrome has shown itself to be different from most other forms of viral pneumonia in its infectivity, clinical course, predilection for affecting health-care workers, and high rates of mortality and morbidity. During the acute phase of the epidemic, the imaging characteristics of SARS during the acute phase have been investigated, but its post-treatment sequelae are only just becoming apparent as they surface in the imaging of patients attending follow-up. In line with the acute stages of this disease, the recovery also appears to be punctuated with an exaggeration of the host response, with patients developing residual disease or early signs of fibrosis in affected areas of the lungs. With this in mind, the follow-up of these patients will require close clinical and radiological monitoring. This chapter shall present the appearances and role of imaging in the follow-up of SARS.

Follow up Presentation of SARS patients

Follow up is usually uneventful for most other types of viral pneumonia in adults. However, while a portion of treated and discharged SARS patients may be completely asymptomatic, a significant number have residual symptoms. It has been reported that 46% of discharged patients complained of exertional dyspnoea at one-month follow-up. This was not restricted to elderly patients but also affected patients in their thirties, resulting in the limitation of their daily activities.

Key Points

Post-treatment SARS patients
A. Asymptomatic (54%)
B. Dyspnoeic (46%)

Pathological Considerations

For the more common viral pneumonia in adults (such as the influenza virus, adenovirus, herpes simplex I and varicella-zoster viruses) despite substantial morbidity, most cases are associated with complete clinical recovery. On the whole, viral pneumonia usually resolves without significant clinical or radiological sequelae. Poor outcome is usually found only at the extremes of age and among the immunocompromised. There are rare exceptions and the consequences range from poor lung function after varicella pneumonia,
adenovirus pneumonia causing bronchiolitis obliterans, to lung fibrosis seen in influenza pneumonia. To these complications we now add SARS-related pulmonary fibrosis.

For SARS, over half (62.5%) of the patients had architectural distortion and other signs of possible fibrosis on early follow up. While this may represent early scarring as a result of the viral infection itself, patients with such changes are found to be those who had a more stormy clinical course and required more intense therapy. The latter suggests that damage may be due to lung inflammation by an exaggerated cell-mediated host immune response elicited by viral antigen, a phenomenon that is apparent during the acute stages of the disease. As a comparison, an exaggerated host response is seen in other complications related to viral infections such as Bronchiolitis Obliterans Organizing Pneumonia (BOOP) and Adult Respiratory Distress Syndrome (ARDS). SARS shares some features with both of these diseases.

- The acute radiological features of SARS, especially those on computed tomography, are similar to those seen in BOOP.
- Some of the SARS patients, especially those with a more stormy in-patient course, develop ARDS like radiographic appearance during the peak of their acute illness.
- Post-mortem of patients who have succumbed to SARS, show changes consistent with ARDS are present in the lungs.
- Pulmonary fibrosis is a known complication of ARDS.

With the above in mind, the possible early fibrosis seen in SARS may indeed be a modified expression of BOOP. Finally, treatment, part of which remains on a trial basis, may also play a significant role on the eventual lung damage.

**Key Points**

- **Pulmonary fibrosis Post-SARS**
- **Possible Causes:**
  - A. Sequelae of infection causing lung damage
  - B. Over-activity of Host Immune Response (SARS, BOOP, ARDS)
  - C. Treatment Side Effect
Role of Imaging in the Follow up of SARS

Chest Radiographs and High Resolution Computed Tomography

The chest radiograph examination is a major diagnostic component endorsed by the World health organization (WHO) and Center of Disease Control and Prevention (CDC) in their guidelines. Thin section or High Resolution Computed Tomography (HRCT) has been helpful in diagnosing the more difficult and probably earlier SARS cases where the chest radiograph is normal. Both modalities have shown themselves useful for monitoring progress and complications during treatment. As a continuation of their role during the acute illness, chest radiographs and fine cut or High Resolution Computed Tomography (HRCT) are the mainstay for the follow up for SARS patients. A study has shown that HRCT was rarely (4.2%) normal in follow up patients with dyspnoea. The same study has also shown how soon (mean follow-up period of 36.5 days after hospital admission and 17.8 days after discharge) HRCT architectural distortion and suggestions of fibrosis may begin in patients with SARS. How much these changes will resolve in future is unknown, although it is unlikely that the areas of severe architectural distortion (Figure 1) will completely disappear. In the more pronounced cases of residual disease, further follow up by radiographs should be sufficient.

Finally, a very small proportion of patients may develop acute symptoms of fever, malaise and increased dyspnoea after discharge. These may be suggestive of incomplete resolution or reactivation of disease. Imaging plays a role in monitoring the lung involvement in these patients in the same manner as for the acute stages of the disease.
**Other types of imaging**

Magnetic Resonance Imaging has so far only had a minor role to play. In our experience, a few patients developed confusion during treatment, and we have performed both CT and MRI of the brain on them. Neither modality showed any abnormality, the confusion in these patients were thus considered to be a side effect of the corticosteroid therapy. In a few treated patients (4 patients at the time of writing this chapter) who developed bone or joint pain during or after their SARS treatment, MRI was performed on the areas of complaint. These were normal except in one patient, where widespread areas of avascular necrosis were present involving both lower limbs (Figures 2 and 3).

**Figure 2**
36-year-old female with no previous illness. Discharged after treatment for SARS. MRI was performed on day 81 (from onset of SARS symptoms). Coronal T1W image of both hips showing avascular necrosis affecting the subchondral bone of both femoral heads.

**Figure 3**
Same patient as Fig. 2. Coronal T1W image of the right knee showing avascular necrosis affecting the marrow of the distal tibial and proximal fibula. Similar changes were present in the other knee.

**Key Points**

**Role of imaging in follow up**
- A. Monitor imaging progress of patients dyspnoeic on follow up
- B. Detection of complication (fibrosis)
- C. Monitor response or complications to drugs
- D. Monitor reactivation of disease
Imaging Appearances

Chest Radiograph
The chest radiograph helps in the diagnosis by demonstrating lung opacities and plays an important role in evaluating the progress of disease and response to treatment. These opacities are usually still present to a variable extent at hospital discharge, keeping in mind that hospital discharge criteria used in our institution are based on:
• being afebrile for at least 96 hours after the last dose of steroid;
• resolving respiratory symptoms and oxygen independence;
• radiological improvement (based on serial chest radiographs);
• improving laboratory parameters.
Evidently, complete resolution of imaging abnormalities is not requisite.

For patients complaining of dyspnoea and exercise intolerance at one month follow up, 83.3% had residual changes on their earlier chest radiograph on day of discharge. But the percentage of abnormals dropped to 62.5% for the radiographs taken at the time of the first month follow up. When comparing the two sets of radiographs, two-thirds of the radiographs taken on the day of discharge showed an improvement at the time of the one-month follow up film, while one third of the abnormal radiographs showed no worsening.

The radiographic abnormalities seen on follow up radiography include (Figure 4):
• ground glass opacification,
• linear opacification,
• pleural/ fissural tethering and evidence of volume loss (seen as shifting of the mediastinal or hilar structures.)

The findings are non-specific and if read in isolation could represent a combination of residual inflammation, atelectasis or fibrosis.

Figure 4
Same patient as the one in Fig. 1, follow up chest radiograph on day 59 (from first day of symptoms). There is diffuse ground glass opacification, linear markings and fissural elevation (arrowheads) in the right upper and mid zone. Elevation of the right hilum indicates volume loss.
**Key Points**

Follow up CXR appearances in treated SARS

A. Complete resolution
B. Ground glass opacification
C. Evidence of Fibrosis: linear opacification, volume loss, pleural tethering
D. Lack of temporal change or resolution.

**High Resolution Computed Tomography**

As previously described, the HRCT findings in SARS for initial diagnosis included:

- ground glass opacification and/or consolidative opacification,
- thickening of inter-lobular septa when present is superimposed on a ground glass opacification, giving a “crazy paving: pattern” \(^9,^{13}\) (Figure 5).
- intra-lobular interstitium thickening
- bronchial dilatation within areas of consolidation (suggesting that it is a form of reactive/respiratory bronchial dilatation).

![Figure 5](image)

25-year-old female, initial HRCT on day 7 (from first day of symptoms). There is ground glass opacification with superimposed smooth thickening of the interlobular septae giving rise to a “crazy paving” pattern (arrow).

For patients who have both an initial and follow up HRCT for comparison progress changes can be expected. There will be a variable degree of resolution of the ground glass
opacification and thickened interlobular septae between the initial and follow up scan. This can be considered to represent imaging evidence of improvement (Figure 6). Resolution of the ground glass opacification suggests the initial lung parenchymal changes are of inflammatory nature and improve after successful therapy.

However, in one study ground glass opacification was present on most (95.8%) follow up HRCTs of dyspnoeic patients. Instead of the uniform density ground glass seen in the initial HRCT, there was variable density between different secondary lobules (Figure 7). This may partly be due to different rates of resolution of the initial fluid/inflammation or may be related to distortion caused by fibrosis. In addition, there was clearing of the subpleural 5mm of the lung, a picture similar to ARDS or pulmonary oedema.

The crazy-paving pattern (Figure 5), so commonly seen in the initial HRCT, is not common in the follow-up HRCT. If thickened septae are present, they are, thinner, distorted and irregular, an appearance more akin to idiopathic pulmonary fibrosis (Figure 8).
On follow up HRCT, signs of fibrosis are (Figure 1 and 9):
- parenchymal bands,
- irregular interfaces (bronchovascular, pleural or mediastinal) and
- traction bronchiectasis.

Thickened interlobular septae or intralobular interstitium should not be used as signs of fibrosis on early follow up as they may represent unresolved interstitial inflammation. The other signs mentioned are however, not present in the initial HRCT used for diagnosis and are thus more reliable. There were signs of fibrosis (parenchymal band, irregular interface and traction bronchiectasis) and peri-bronchovascular interstitial thickening (Figure 1) in 62.5% of dyspnoeic patients on early follow up. These were associated with architectural distortion resulting in rotation of the fissures and bronchovascularature. The ground glass opacification in these patients surrounded the areas of fibrosis.

Consolidation is not a common feature of SARS on follow up HRCT. Only very small areas of consolidation were seen in follow up HRCT and when present are around thickened
bronchi (Figure 10). There are also small patches of consolidation in the center of the fibrotic areas, adjacent to the bronchi.

Figure 10
36-year-old male treated and discharged. Follow up HRCT on day 44 (from first day of symptoms). There is peri-bronchovascular thickening and patchy areas of ground glass opacification (arrow) and irregular interlobular septal thickening (arrowheads).

There were no masses or nodules, emphysema, cavitation or calcification present.

Key Points
Follow up HRCT appearances in treated SARS
A. Complete resolution
B. Patchy ground glass opacification
C. Evidence of Fibrosis: architectural distortion, parenchymal bands, irregular interfaces (bronchovascular, pleural or mediastinal) and traction bronchiectasis.

Key Points
Comparison between initial and follow up HRCT

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<tr>
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<th>Initial HRCT</th>
<th>Follow up HRCT</th>
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<tbody>
<tr>
<td>Ground glass opacification</td>
<td>uniform density</td>
<td>variable density, subpleural clearing</td>
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<tr>
<td>Septal thickening</td>
<td>unifrom &amp; thick</td>
<td>irregular &amp; thin</td>
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<tr>
<td>Architectural distortion</td>
<td>absent</td>
<td>present</td>
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<tr>
<td>Parenchymal bands</td>
<td>absent</td>
<td>present</td>
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<tr>
<td>Irregular interfaces</td>
<td>absent</td>
<td>pleural, mediastinal bronchovascular</td>
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<td>Bronchial dilatation</td>
<td>respiratory</td>
<td>traction</td>
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In SARS patients with follow up HRCT evidence of fibrosis, the significance of the concomitant ground-glass opacification is not clear. If Bronchiolitis Obliterans Organizing Pneumonia (BOOP) or forms of idiopathic interstitial pneumonia are used as a frame of reference \(^{14,15}\), these changes may represent persistent inflammation that is potentially reversible upon treatment. Currently, treatment with corticosteroid or other steroid-sparing immuno-modulating agents (such as cyclophosphamide) have been used in BOOP \(^{16,17}\). These are being tried for SARS induced fibrosis. Hence the role of HRCT in follow-up of SARS patients is to assess the extent of long-term lung parenchymal injury/fibrosis and to identify these potentially reversible components early so that appropriate treatment may be instituted to prevent further lung damage. It also plays a role in monitoring the disease response and development of complications in drug trials.

The early abnormalities detected on radiographs and HRCT must be interpreted with caution. While some of the changes obviously represent parenchymal fibrosis, others may represent potentially atelectasis and inflammatory exudate. Although the absolute identity of these lesions is as yet unknown, the possibility that there may be a reversible component warrants continuation of treatment to halt or minimize fibrosis and to monitor progress. This is where follow up imaging is mandatory in the group of patients developing short to medium term symptoms. More long-term studies are needed to properly define fibrosis in SARS and the ultimate appearance.

**Patients with major complications**

**Intensive care patients:**

A minority of patients survive a very stormy course in the Intensive Care Unit before recovery. These patients understandably have more abnormalities on their discharge chest radiographs and HRCT (Figure 11).

**Figure 11**

54-year-old male in the intensive care unit. HRCT on day 67 from first day of symptoms (day 53 from the onset of ARDS). Loculated pneumothorax was present (arrow). There are parenchymal bands, irregular interfaces (arrowheads).
In addition, some of these SARS patients have progressed to ARDS during the peak of their illness, as may occur in other types of viral pneumonia \(^{18}\). Fibrosis, to the extent of honeycombing, is known to occur in patients who have survived Acute Respiratory Distress Syndrome and there is evidence that the same may occur in some of the SARS patients. In particular, cystic changes are seen in some of the SARS patients who have developed ARDS during their acute illness (Figures 12 and 13). These cysts are similar to those seen after ARDS of other causes \(^{19}\) and are not a feature in the HRCTs from other SARS patients who did not develop ARDS during their acute illness \(^{2}\).

**SARS patients with evidence of lung fibrosis**

Dyspnoeic patients with follow up HRCT early evidence of fibrosis were relatively older males \(^{2}\). These patients also possess the worst initial HRCTs and the worst appearing chest radiographs during treatment. These most likely reflect that these patients suffered a more severe course than those who did not develop evidence of early fibrosis.
Patients with HRCT evidence of fibrosis also had a higher requirement of pulse intravenous methylprednisolone during treatment. This is on top of the combination of oral Ribavirin and oral corticosteroids used on all patients. High dose corticosteroid in the form of pulse therapy was given to patients not responding favorably to the standard combination. The need of pulse steroid therapy gives a reflection of the magnitude of the cytokine storm elicited by the viral antigen, which in fact may be the underlying pathogenesis of lung damage and subsequent development of fibrosis. The peak Lactate Dehydrogenase (LDH) level is also higher in these patients. LDH is an indicator of tissue destruction (presumably lung tissue in SARS) and has shown to be a good independent predictor of worse clinical outcome.

**Key Points**

**SARS fibrosis patient profile**

A. Older (average age 45 year old)  
B. Majority of worst cases involve males  
C. Worst initial HRCT  
D. Worst serial chest radiographs  
E. Higher pulse steroid requirement  
F. Higher peak LDH

**Protocol for Follow up Imaging**

Chest radiographs could be performed on standard equipment using the established routine. For HRCT we use 1mm thick slices with 6mm gap, scanning the patient supine and inspiration. Exposure parameters were set at 1sec, 120kV, 140mA.

A. A baseline chest radiograph should be performed on hospital discharge. HRCT may be added on discharge if there are marked radiographic abnormalities, if the patient is breathless or if the clinical course was severe.

B. For dyspnoeic patients, monthly chest radiographs performed just prior to follow up clinic. This may need to be more frequent warranted by the patients’ condition or if trial treatment is commenced.

C. HRCT at 6 months follow up if a discharge HRCT was required.

D. Further imaging follow up if clinically required.
Conclusion

Pulmonary fibrosis may develop early in a substantial proportion of SARS patients who have been discharged after treatment. Patients who are older and have more severe disease during treatment are more likely to develop HRCT findings of fibrosis. The role of imaging in the follow up of SARS patients should be focused on these patients. Imaging follow up will provide information on the progress of disease, a guide to treatment response and demonstrate complications that may arise.
References