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TITLE:

Imaging Features of Systemic Sclerosis-Associated Interstitial Lung Disease

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SUMMARY:

Here, we present practical recommendations for performing thoracic high-resolution computed tomography for diagnosing and assessing systemic sclerosis-related interstitial lung disease.

ABSTRACT:

Early diagnosis of systemic sclerosis-related interstitial lung disease (SSc-ILD) is important to enable treatment to be administered with minimal delay. However, diagnosing SSc-ILD is challenging because key symptoms are non-specific. High-resolution computed tomography (HRCT) of the chest is recognized as a sensitive imaging method for diagnosing and assessing SSc-ILD. Exposure of patients to ionizing radiation may be considered as a limitation, although methodological steps may be taken to moderate this. We present practical recommendations for performing HRCT scans and interpreting the results. Key features of SSc-ILD on HRCT include a non-specific interstitial pneumonia (NSIP) pattern with peripheral ground-glass opacities and extensive traction bronchiectasis. Despite similarities between SSc-ILD and idiopathic pulmonary fibrosis (IPF), HRCT can be used to differentiate between these conditions: in SSc-ILD compared with IPF, there is a greater proportion of ground-glass opacity and fibrosis is less coarse. A dilated, air-filled esophagus with diameter >10 mm, suggestive of esophageal dysmotility is commonly seen in SSc-ILD. Pulmonary artery size greater than the adjacent ascending aorta suggests coexistent pulmonary hypertension. Nodules must be monitored due to the increased risk of lung cancer. A large extent of disease on HRCT (≥20%) or a high fibrosis score suggests an increased risk of mortality. HRCT is central to diagnosing SSc-ILD, and serial assessments can be helpful in monitoring disease progression or treatment response.

INTRODUCTION:

Systemic sclerosis (SSc) is a complex, heterogeneous, autoimmune disease. It may be manifested as vasculopathy, Raynaud's phenomenon and fibrosis of the skin and internal organs[1]. SSc is classified into subtypes as follows: limited cutaneous, diffuse cutaneous, sine scleroderma (without skin involvement), and SSc overlap syndrome[1].

SSc is not inherited in Mendelian fashion, but genetic factors appear to influence susceptibility to the disease. Incidence rates differ between ethnic groups and are increased among individuals with a family history of the disease[2,3]. Environmental risk factors also appear to exist, with high exposure to silica or organic solvents appearing to increase the occurrence of SSc[4]. The global prevalence of SSc is around 1 in 10,000[1]. More females than males are affected by SSc, with reported female:male ratios ranging between 3:1 and 8:1, and the age group with the highest incidence of the disease is 45–54 years[5].

The lung is the second most commonly affected visceral organ in patients with SSc[6]. There are two main pulmonary manifestations of SSc: interstitial lung disease (ILD), and pulmonary hypertension[7]. ILD is usually fibrotic; it occurs in approximately 80% of patients with SSc and is more common in diffuse cutaneous scleroderma than in the limited form of the disease[1,8]. Pulmonary hypertension may manifest as isolated pulmonary arterial hypertension (PAH, which has a prevalence of 13–35% in SSc) or pulmonary hypertension resulting from left ventricular involvement/diastolic dysfunction or ILD/hypoxemia[7]. Antibody profiles differ between patients with SSc-ILD and those with SSc-PAH. For example, the presence of anti-Scl-70 antibodies is associated with SSc-ILD[8], while anticentromere antibodies are more common in SSc patients with PAH than in those without PAH[9].

The symptoms of SSc-ILD include dyspnea, coughing, chest pain, and exercise limitation. ILD is a major contributor to morbidity in SSc[10-12]. As a consequence, annual all-cause healthcare costs have been reported to be higher in patients with SSc-ILD than in those with SSc and no ILD: $31,285–55,446 versus $18,513–23,268, respectively[13].

SSc-ILD is the leading cause of mortality in patients with SSc, accounting for 30–35% of deaths in this group[10,14]. Median survival among patients with SSc-ILD has been reported to be 5–8 years[10,15]; by comparison, approximately 76% of the overall population with SSc survive for more than 10 years from disease onset[16]. Significant predictors of mortality in SSc-ILD include age, forced vital capacity (FVC), baseline diffusing capacity of the lung for carbon monoxide (DLCO), extent of disease on high-resolution computed tomography (HRCT), presence of pulmonary hypertension and levels of Kerbs von den Lungren 6 (KL-6) antigen[17,18].

Early diagnosis is important to enable treatment to be administered with minimal delay and, in patients with a progressive phenotype, disease progression may potentially be slowed. However, diagnosing SSc-ILD is challenging because non-specific symptoms of cough, dyspnea, and fatigue can be mistaken for other aspects of SSc, such as cardiac disease and musculoskeletal involvement. Evaluations for diagnosing ILDs include: clinical presentation, history, smoking status, lung function, imaging, and in some cases, lung biopsy. Affirmation of

SSc-ILD diagnosis requires several investigations, which are often used in combination[19]. The most frequently used assessments include pulmonary function tests and HRCT[20-23]. Other imaging methods, such as chest radiography and radiation-sparing imaging (e.g., magnetic resonance imaging [MRI], lung ultrasound) may also be employed[22]. Pulmonary function tests are used to assess the severity of the ILD and monitor its course. However, the use of pulmonary function tests alone is of limited use for diagnosing SSc-ILD[24,25]. HRCT of the chest is viewed as the most sensitive non-invasive means of facilitating differential diagnosis of SSc-ILD[19]. Baseline HRCT results, as well as changes over time, can be used to predict the future course of lung disease and potential response to therapy[26].

Exposure to radiation with HRCT is sometimes considered as a limiting factor for regular screening[27,28]; limiting the number of slices is a potential method for reducing the radiation risk, and the dose may also be reduced by decreasing either the voltage or the current[29-31]. Alternatively, different assessment methods may be considered. For example, MRI appears to have some potential for evaluation and follow-up of ILD patients[22]. In one study using T2-weighted MRI images with respiratory synchronization, HRCT was performed in parallel as the 'gold-standard' assessment; 100% sensitivity and 60% specificity were reported with MRI for determining the presence of ILD[32]. Similar agreement between MRI and HRCT in the detection and categorization of ILD was reported in another study[33]. Despite the promising results, MRI is currently a research methodology and it is not yet ready for generalized clinical use.

Here, we provide a practical overview of the interpretation of imaging results, with a focus on HRCT, for diagnosing lung involvement in SSc, determining prognosis, and also exploring future developments that may improve imaging methods and interpretation of results. HRCT images from representative cases are included in the paper.

PROTOCOL:

1. HRCT scanning

1.1. Perform volumetric HRCT acquisition scanning of the chest[36]. Contrast agents are not required[36,37].

1.2. Obtain the following acquisitions with parameters shown in **Table 1**[36,37].

1.2.1. Acquire a supine inspiratory scan (volumetric) from the lung apices to the lung base.

1.2.2. Acquire a supine expiratory scan (sequential with 10–20 mm gaps) from 2 cm below the lung apices to the lung base.

1.2.3. Acquire a prone inspiratory optional (sequential with 10–20 mm gaps) from the carina to the lung base.

1.3. Give breathing instructions to the patient before each acquisition[36,37]. For an inspiratory

scan, say "Take in a deep breath….and let it out. Take in another deep breath….and let it out. Take in another deep breath, and hold your breath in. Keep holding your breath"[37].

1.4. Obtain inspiratory scans at full inspiration[35,36].

1.5. Use the thinnest collimation, shortest rotation time and highest pitch to ensure that motion-free images are obtained[36]. Suggested scanning parameters are detailed in **Table 1**[37].

1.6. For optimal quality of volumetric scans, obtain thin section (<2 mm) images with high-spatial resolution reconstruction[35,36].

1.7. Review scans immediately after acquisition and repeat if either motion artifact is present or inadequate inspiration has occurred[37].

2. Reporting

2.1. Prepare an interpretive report.

2.2 Share the report and HRCT images with the patient's care team and add them to the patient's medical records.

REPRESENTATIVE RESULTS:

Diagnosis

Key features of SSc-ILD on HRCT commonly include a non-specific interstitial pneumonia (NSIP) pattern with peripheral ground-glass opacities and extensive traction bronchiectasis (**Figure 1** and **Figure 2**). Ground-glass opacities have a broad etiology and are often non-specific[40-42]. Central predominance or peripheral distribution with subpleural sparing is highly suggestive of NSIP (**Figure 3**).

Typically, ILD patterns in HRCT images include reticulations with architectural distortion resulting in traction bronchiectasis/bronchiolectasis (consistent with a fibrotic form of NSIP). Indeed traction bronchiectasis and traction bronchiolectasis are often the predominant features of SSc-ILD (**Figure 4**)[43]. Additional findings may include honeycombing (**Figure 5**; more common in limited forms of SSc), interlobular septal thickening and intralobular lines, and micronodules[40,44]. Honeycombing refers to clustered cystic airspaces of typically consistent diameter (~3–10 mm) with thick, well defined walls[31]. Honeycombing and traction bronchiectasis are key features of usual interstitial pneumonia (UIP) on HRCT. Although this pattern is most commonly associated with idiopathic pulmonary fibrosis (IPF), the prototype fibrosing ILD with a progressive phenotype, it can sometimes be seen in patients with SSc-ILD[10]. Recently, several signs have been identified in patients with connective tissue disease-related ILD (including SSc-ILD) and the UIP pattern on HRCT, but not in those with IPF. These are the straight edge sign (i.e., isolation of fibrosis to the lung bases with sharp demarcation in the craniocaudal plane without substantial extension along the lateral margins of the lungs on coronal images), the honeycombing predominant (or exuberant) sign (>70% of fibrotic portions

of the lung), and the anterior upper lobe sign (i.e., concentration of fibrosis within the anterior aspect of the upper lobes, with relative sparing of the other aspects of the upper lobes, and concomitant lower lobe involvement)[45]. The straight edge sign has also been associated with NSIP pathology[46], which is the main CT pattern in SSc-ILD[10].

Dilated air-filled esophagus is frequently observed in patients with SSc (**Figure 6**)[47-49] and in patients with SSc-ILD[47,48]. While there is no accepted upper age limit where a dilated esophagus may no longer help to differentiate SSc-ILD and IPF, a dilated esophagus may be more difficult to interpret in patients over age 65 due to increasing incidence of esophageal motility disorders. Mediastinal lymphadenopathy (usually reactive), in which the short axis of the lymph node exceeds 10 mm, is also often observed in patients with SSc-ILD[47,50]. Pulmonary artery size greater than the adjacent ascending aorta suggests coexistent pulmonary hypertension (**Figure 6**), even in patients without fibrotic lung disease[51-53]. Areas of consolidation suggest superimposed infection, aspiration, organizing pneumonia, hemorrhage or malignancy. Nodules must be monitored due to the increased risk for lung cancer in SSc-ILD[7]; the most common primary cancer to arise in patients with SSc-ILD is adenocarcinoma[7,54].

SSc-ILD shares a number of clinical, mechanistic, and pathological similarities with IPF[15,55]. However, some radiologic features allow the differentiation of these two ILDs[15,45]. In SSc-ILD, compared with IPF, there is a greater proportion of ground-glass opacity and fibrosis is less coarse. In cases of UIP in SSc, honeycombing may be observed in more than 70% of the fibrotic-lung tissue – the exuberant honeycombing sign[56,57]. In addition, the four-corners sign (also known as the anterior upper lobe sign) is significantly more common in SSc-ILD than in IPF; this is a pattern of inflammation and/or fibrosis focally or disproportionately involving the bilateral anterolateral upper lobes and posterosuperior lower lobes[58].

Chest radiographs may initially detect ILD; however, they do not offer enough contrast resolution for reliable diagnosis. In chest radiographs from patients with SSc-ILD, the most frequent pattern is basal predominant reticulation[59]. Further features may include visible bronchiectasis, volume loss and honeycombing. As with HRCT, the presence of a dilated air-filled esophagus may be helpful in supporting the diagnosis of SSc-ILD[47].

Prognosis

Several different imaging findings have been shown to be associated with prognosis in SSc-ILD. Mortality risk has been reported to be higher in patients with a disease extent of at least 20% on HRCT (10-year survival was 43% versus 67%, respectively, in patients with disease extent above versus below the 20% threshold)[60]. Similarly, a high fibrosis score on HRCT (based on the extent of reticulation and honeycombing) has been associated with increased mortality[61]. Large esophageal diameters are associated with increased ILD severity and decreased DLCO[48]. Lung density and pulmonary artery diameter may potentially be used to predict the risk of pulmonary hypertension[62]. Computerized, quantitative CT parameters could also be harnessed to identify patients' risk of lung function decline or mortality. One study suggested that the extent of ILD, quantified from HRCT, could be used to predict the decline in FVC over 12 months[63]. In another study, quantitative chest CT parameters provided mortality risk results

that were consistent with clinical prediction models[64]. Despite their apparent potential, imaging-based biomarkers are currently best considered at a population level as their clinical utility in individual patients has not been established.

Treatment response

Cyclophosphamide and mycophenolate mofetil provide modest benefit in patients with SSc-ILD. In the landmark Scleroderma Lung Study I, cyclophosphamide treatment led to slower progression of fibrosis compared with placebo[65]. More recently, the Scleroderma Lung Study II reported similar efficacy and improved tolerability with mycophenolate mofetil in comparison with cyclophosphamide[66]. However, there remains a need for improved treatment options for patients with SSc-ILD. Therapies currently being investigated include monoclonal antibodies (e.g. rituximab, abituzumab), antifibrotic agents (e.g., nintedanib, pirfenidone), the direct thrombin inhibitor dabigatran, the proteasome inhibitor bortezomib, and hematopoietic stem cell transplantation[19,67].

Serial HRCT scans showing disease progression in a patient with SSc-ILD

HRCT assessments performed at different timepoints may be used to investigate disease progression. **Figure 7** shows two sets of axial and coronal chest HRCT images taken 10 years apart in a patient with SSc-ILD. The initial axial and coronal images (**Figure 7A,B**) from chest HRCT show basilar predominant ground-glass opacity and reticulation with mild traction bronchiectasis and subpleural sparing consistent with NSIP in this patient with SSc. The latter set of images (**Figure 7C**, **D**) taken 10 years later, show increased reticulation and traction bronchiolectasis at the lung bases with decrease in ground-glass opacity on axial and coronal (**Figure 7C,D**) images from chest CT consistent with mild worsening of pulmonary fibrosis. Serial HRCT scans can also be used to monitor treatment response[68-70]; this was demonstrated in the Scleroderma Lung Study II, in which computer-aided diagnosis scores based on HRCT scans were used to compare the efficacy of cyclophosphamide with mycophenolate mofetil in patients with SSc-ILD[68].

Table 1: Computed tomography acquisition parameters[37]. N/A = not applicable.

Figure 1: Systemic sclerosis with a cellular NSIP pattern of disease. Axial (**A**), prone (**B**) and coronal (**C**) high-resolution computed tomography images all show extensive peripheral and basal predominant ground-glass opacities; these are typical observations with NSIP. The lack of traction bronchiectasis is suggestive of a cellular NSIP pattern of disease. NSIP = non-specific interstitial pneumonia.

Figure 2: Systemic sclerosis with a fibrotic non-specific interstitial pneumonia pattern of disease. Axial computed tomography image shows extensive, basal-predominant ground-glass opacities with associated traction bronchiectasis. Notably, the esophagus shows marked dilation; this is typical of scleroderma.

Figure 3: Systemic sclerosis with a fibrotic NSIP pattern. Axial high-resolution computed tomography images (**A and B**) show extensive ground-glass opacities, reticulation, architectural

distortion and traction bronchiectasis. Notably, subpleural sparing is apparent; this is typical of NSIP and is seen in about 50% of all cases. NSIP = non-specific interstitial pneumonia.

Figure 4: Systemic sclerosis with exuberant traction bronchiectasis. Axial (**A**) and coronal (**B**) high-resolution computed tomography images show extensive middle and lower lung zone predominant traction bronchiectasis. While this may be mistaken for honeycombing, the cystic areas connect with each other and spare the immediate subpleural lung; this is typical of bronchiectasis.

Figure 5: Systemic sclerosis with a UIP pattern of lung fibrosis. Axial (**A**) and coronal (**B**) computed tomography images show peripheral and basal predominant honeycombing and traction bronchiectasis in keeping with the typical UIP pattern of lung fibrosis. Note the dilated esophagus (attributable to scleroderma) and the 'exuberant' honeycombing (suggestive of ILD related to connective tissue disease rather than idiopathic pulmonary fibrosis). UIP = usual interstitial pneumonia.

Figure 6: Systemic sclerosis with pulmonary hypertension and dilated esophagus. Contrast-enhanced chest computed tomography shows marked enlargement of the pulmonary trunk, with a larger measurement than the adjacent ascending aorta that suggests underlying pulmonary hypertension. The esophagus is markedly dilated; this is attributable to scleroderma.

Figure 7: Serial chest HRCT images showing progression of pulmonary fibrosis in patient with SSc-ILD. Axial (**A**) and coronal (**B**) images from chest HRCT show basilar predominant ground-glass opacity and reticulation with mild traction bronchiectasis and subpleural sparing consistent with non-specific interstitial pneumonia in this patient with SSc. After 10 years, increased reticulation and traction bronchiolectasis at the lung bases with decrease in ground-glass opacity are observed on axial (**C**) and coronal (**D**) chest HRCT images, consistent with mild worsening of pulmonary fibrosis. HRCT = high-resolution computed tomography; SSc-ILD = systemic scleroderma-associated interstitial lung disease.

DISCUSSION:

While HRCT is currently the definitive imaging method for diagnosing and assessing SSc-ILD, it uses ionizing radiation and is relatively expensive. Chest radiographs may be undertaken instead, although these do not facilitate differential diagnosis to the same extent as HRCT, and a normal chest radiograph does not eliminate the possibility of ILD. Perhaps the best use of chest radiographs is to monitor for progressive disease between HRCT scans and for the exclusion of complicating disease, such as infectious pneumonia, in the setting of acute worsening of symptoms.

A perceived limitation of HRCT is radiation exposure. As described earlier, new methods of conducting CT scans may enable radiation exposure to be reduced[31], and furthermore, current CT scanners provide an array of advanced techniques that offer the possibility in the future to lower radiation exposure to nearly chest radiograph levels. Alternatively, imaging methods such as MRI or lung ultrasound could potentially be used to avoid exposing the patient to radiation in

the future[32,71-73]. We believe that, while there are risk-benefit considerations associated with imaging utilization, the advantages of CT in diagnosis and patient management far outweigh the potential risks.

Imaging data, particularly HRCT, provide arguably the most important information to enable diagnosis of SSc-ILD. Detailed consideration of the patterns and features of HRCT scans is usually sufficient to distinguish SSc-ILD from other lung diseases, with the benefit of avoiding the need for an invasive biopsy procedure.

Visual assessment of HRCT scans introduces a degree of subjectivity and the possibility of inter-observer variability. Computer-based methods of HRCT scan interpretation have been investigated as a possible approach to improving accuracy[63,74]. For example, quantitative approaches to the assessment of lung fibrosis or the extent of disease may be used to assess treatment response[68,70,75]. However, these methods are not widely used in daily clinical practice at this time.

We hope the information presented in this manuscript will serve as a practical guide to assist physicians in using HRCT scans for diagnosing SSc-ILD and determining prognosis. Improved methods for obtaining images and for interpreting scans have the potential to reduce patients' exposure to radiation and improve diagnostic/prognostic accuracy.

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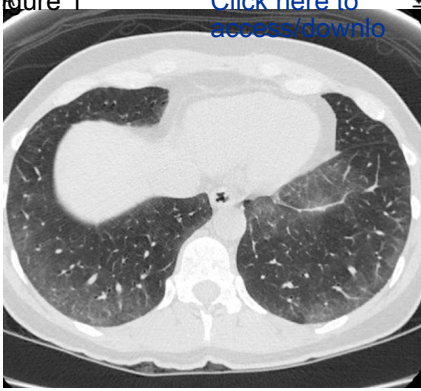

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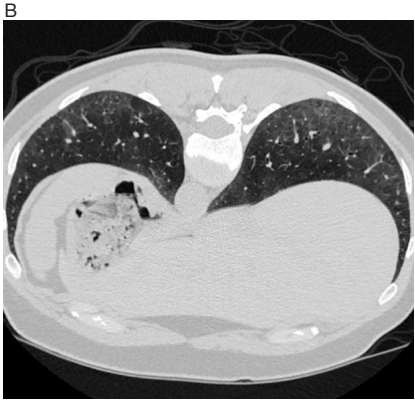

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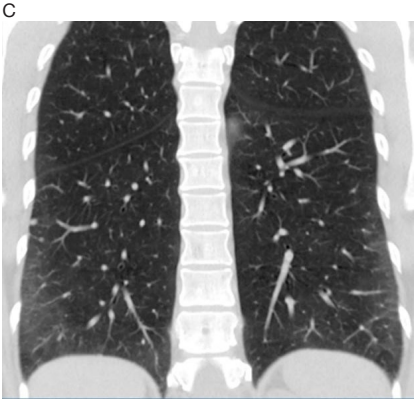

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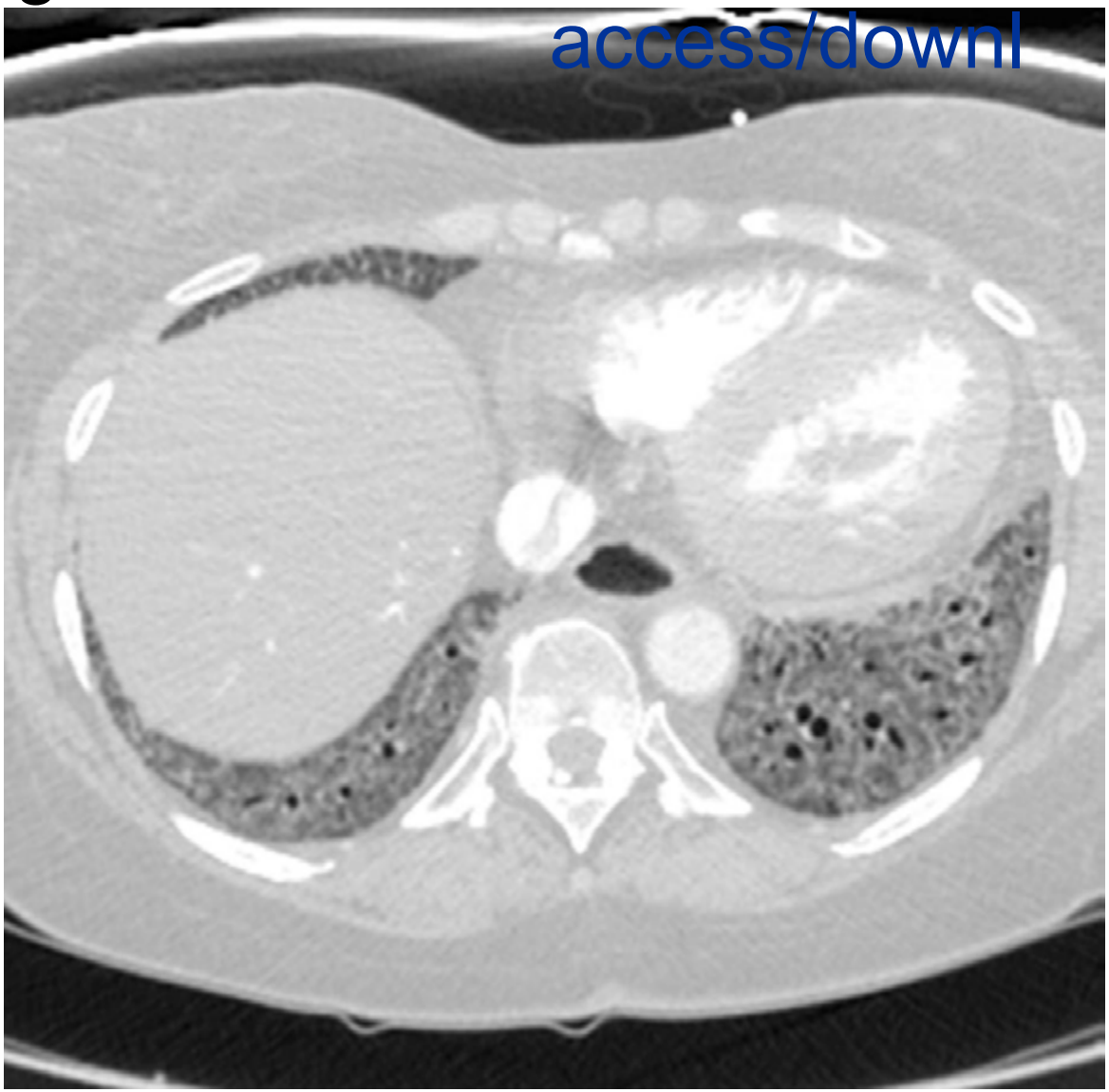

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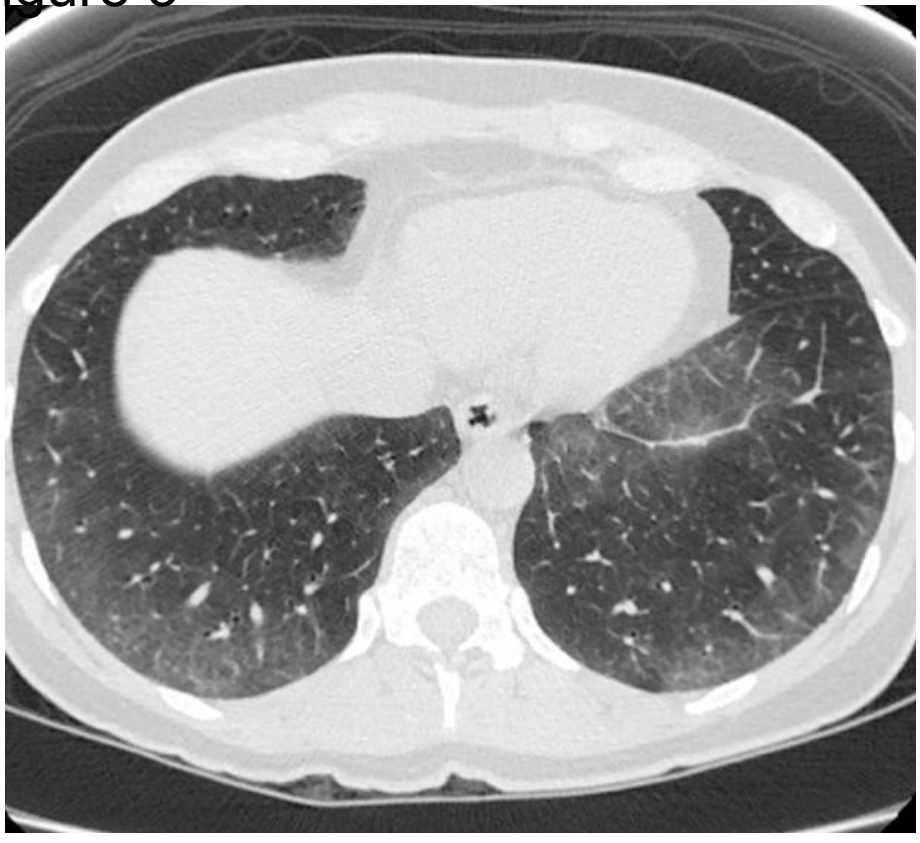

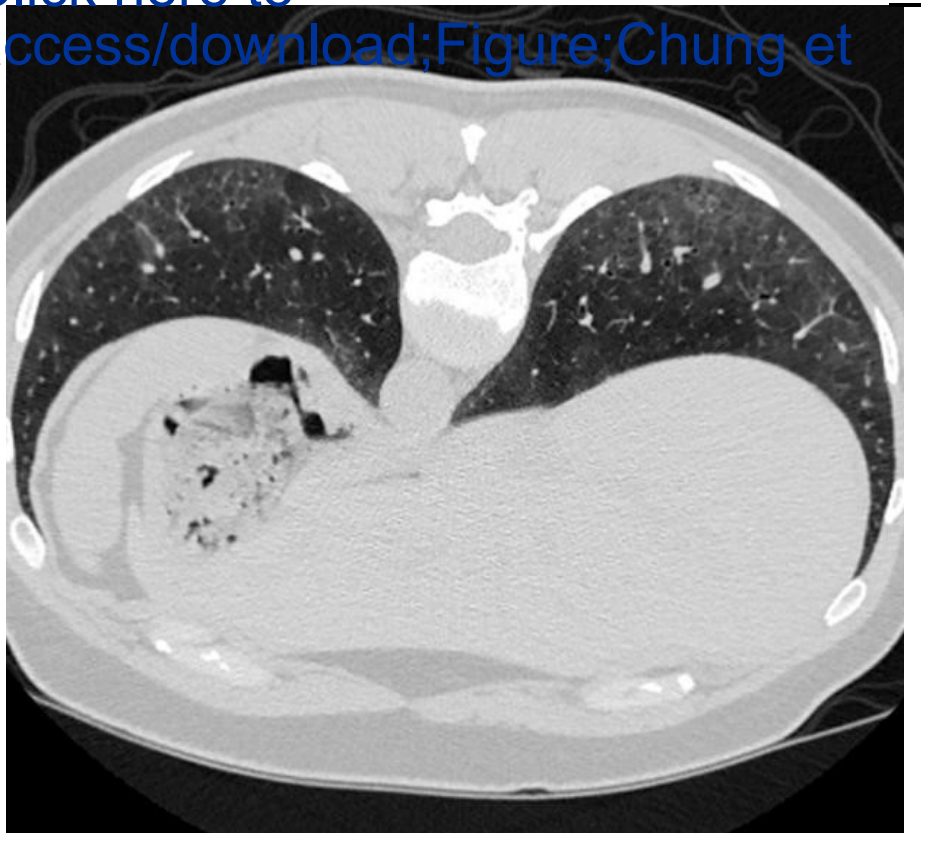

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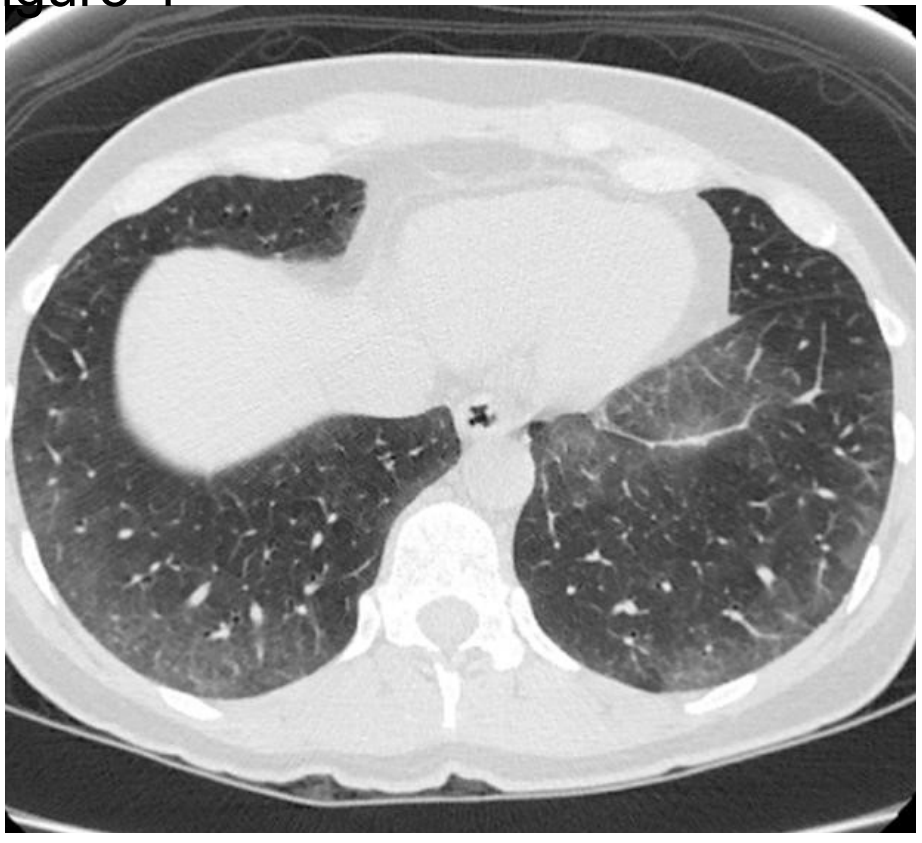

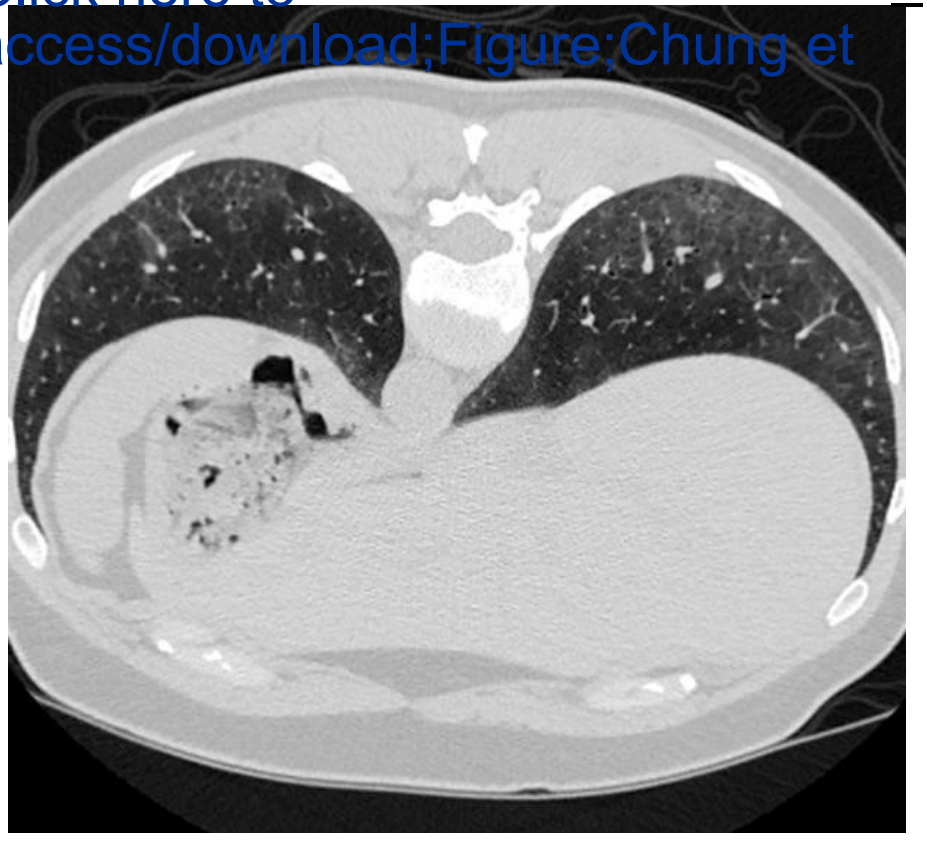

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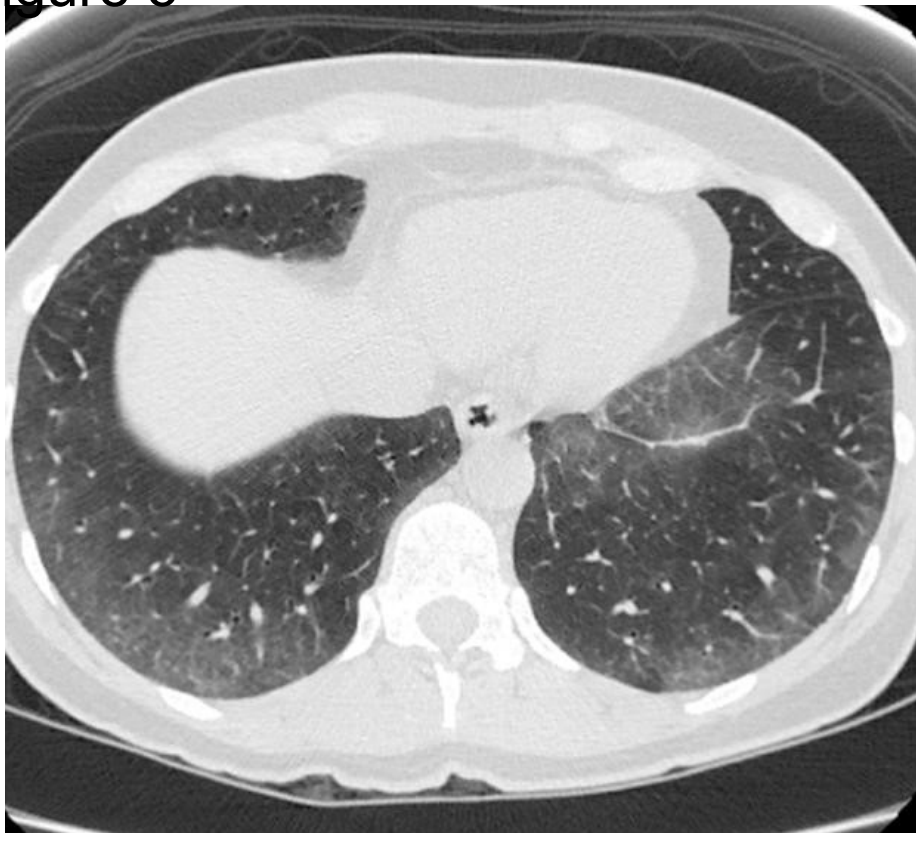

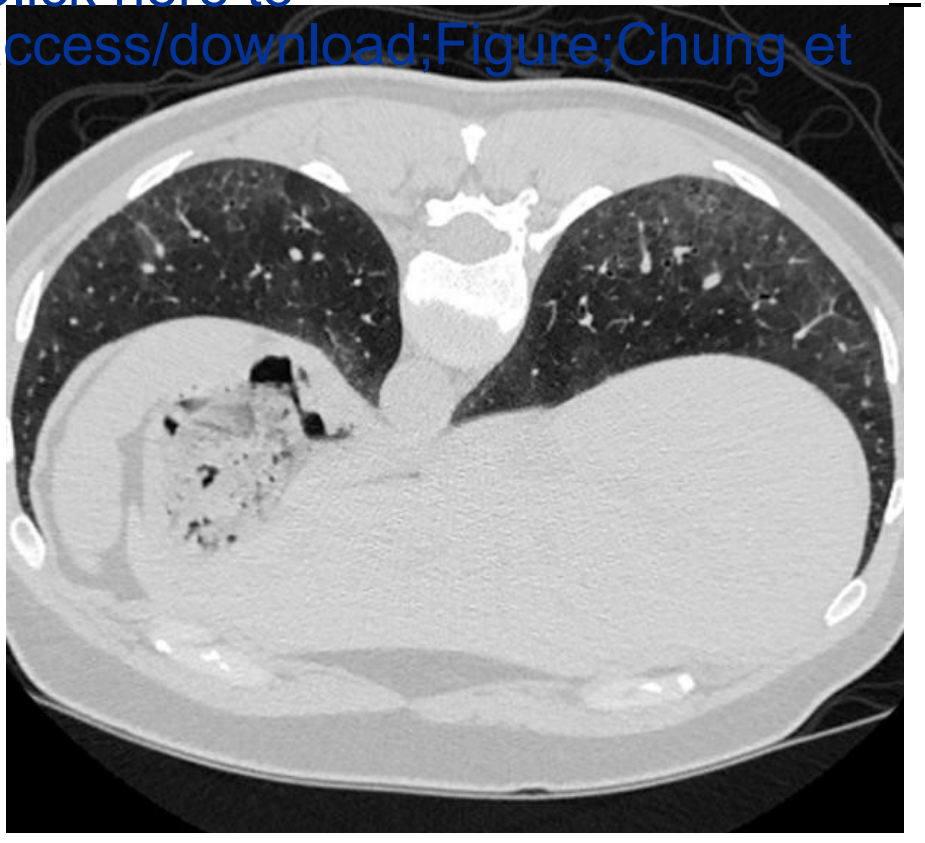

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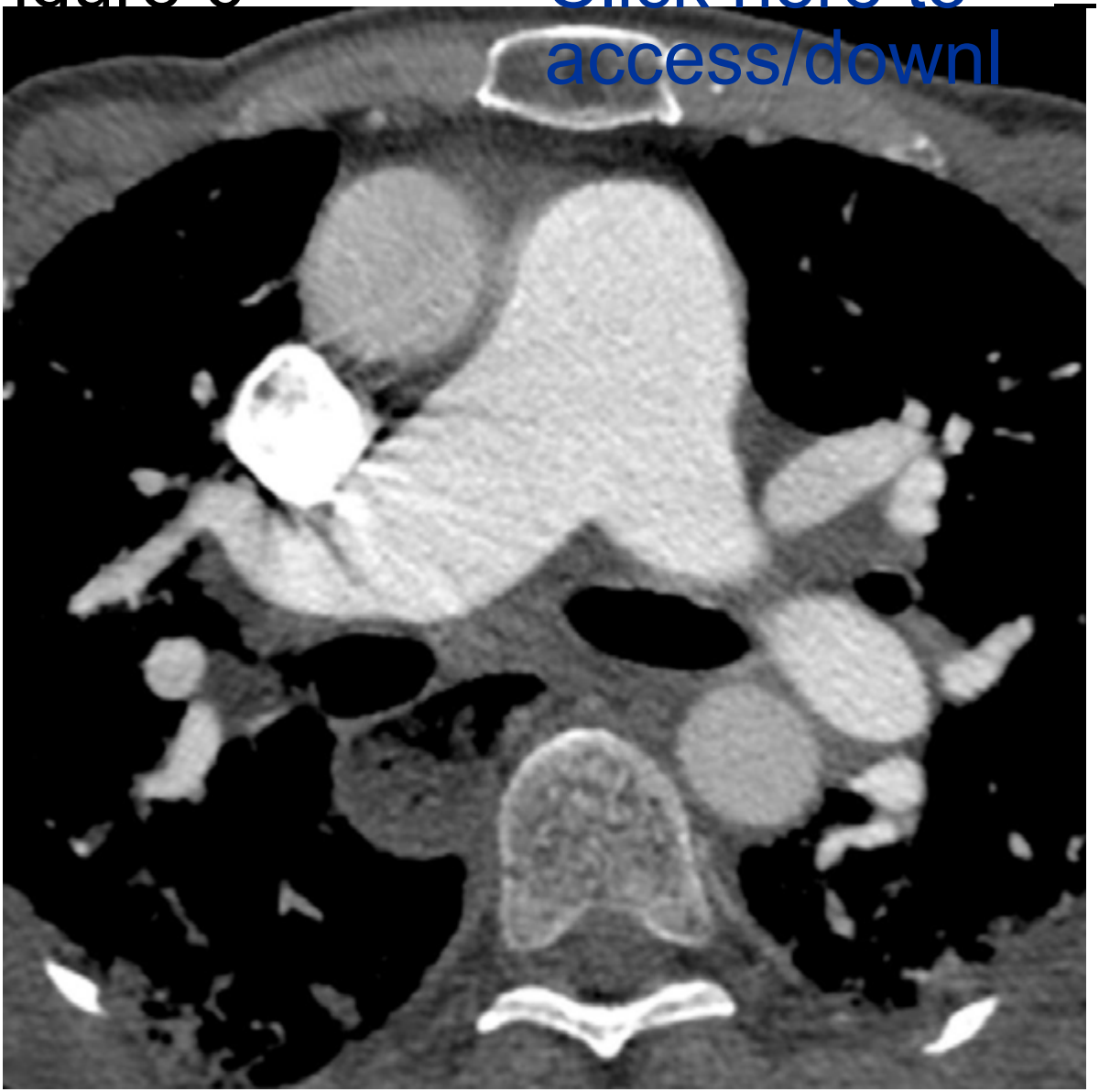

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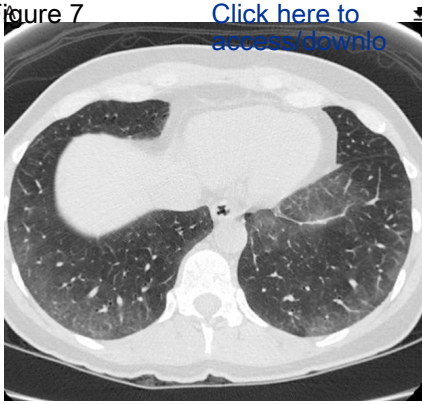

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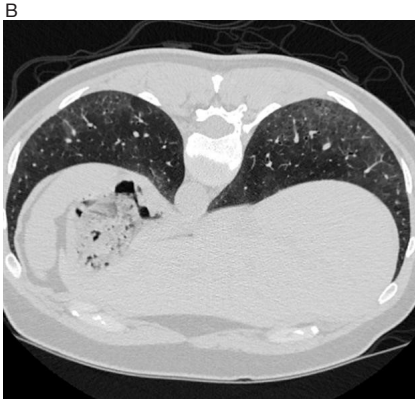

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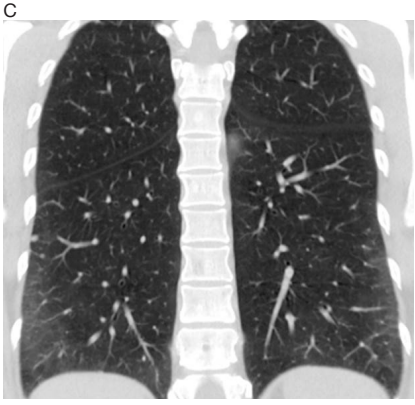

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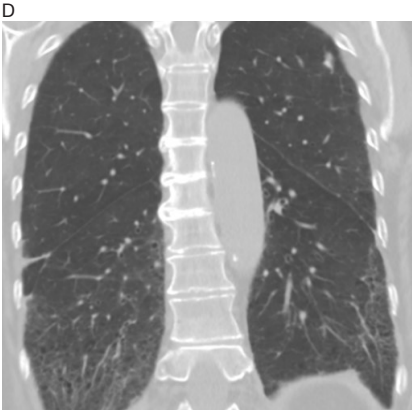

Table

Phase	Detector collimation	Voltage (kV)	Current (mAs)	Scan interval
Supine inspiratory	Helical 1.2 mm	120 (may be lowered)	230 (may be lowered)	N/A
Supine expiratory	Axial 2 x 1.0 mm	120	150	20 mm
Prone inspiratory	Axial 2 x 1.0 mm	120	150	20 mm

Pitch	Rotation	Tube current modulation
~1.0	0.5 seconds or faster	On
N/A	1.0 seconds	On
N/A	1.0 seconds	On

Table of Materials

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Name of Material/Equipment	Company	Catalog Number	Comments/Description
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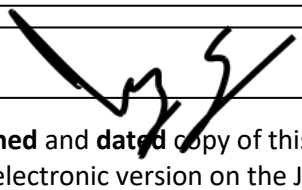
Signature:	
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"Imaging Features of Systemic Sclerosis-Associated Interstitial Lung Disease"

Editorial Comments:

• Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammatical errors.

Response: We confirm that the manuscript has been proof read prior to resubmission.

• **Protocol Language:**

1) The JoVE protocol should be almost entirely composed of numbered short steps (2-3 related actions each) written in the imperative voice/tense (as if you are telling someone how to do the technique, i.e. "Do this", "Measure that" etc.). Any text that cannot be written in the imperative tense may be added as a brief “Note” at the end of the step (please limit notes). Please re-write your ENTIRE protocol section accordingly. Descriptive sections of the protocol can be moved to Representative Results or Discussion. The JoVE protocol should be a set of instructions rather a report of a study. Any reporting should be moved into the representative results.

Response: The protocol has been rewritten in the imperative tense as requested by the journal. Descriptive sections of text have been moved to other sections where necessary.

2) Currently the protocol is described as a list of recommendations. The protocol should be re-written as a set of **specific instructions** describing a clear workflow/procedure.

Response: The protocol has been rewritten in the imperative tense as requested by the journal.

3) Please split up the protocol into subsections for better readability.

Response: The protocol has been divided into subsections for better readabilty.

• Please include an ethics statement before your numbered protocol steps indicating that the protocol follows the guidelines of your institutions human research ethics committee.

Response: This is a clinical practice protocol, and not a research protocol with IRB/ethics approval. In addition, given no patient data have been used in this review article, we believe an ethics statement does not apply in this case.

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Response: The protocol content has been revised.

• **Discussion:**

JoVE articles are focused on the methods and the protocol, thus the discussion should be similarly focused. Please ensure that the discussion covers the following in detail and in paragraph form (3-6 paragraphs): 1) modifications and troubleshooting, 2) limitations of the technique, 3) significance with respect to existing methods, 4) future applications and 5) critical steps within the protocol.

Response: The paragraphs in the Discussion have been reviewed and reorganized in line with the reviewer comments.

• **Figures:**

1) Please provide each figure (if multiple panels are present per figure, keep them within 1 file) as an individual SVG, EPS, AI, TIFF, or PNG file.

Response: Figures have been saved as PNG files.

2) Please provide scale references on the Ct images where possible.

Response: Thank you for this comment. It is not standard for any radiology imaging publications to include scale references, and we are unable to provide them.

• **References:** Please spell out journal names.

Response: The reference list has been updated following the revisions made to the text. Journal names have been updated per the editorial comment.

• If your figures and tables are original and not published previously or you have already obtained figure permissions, please ignore this comment. If you are re-using figures from a previous publication, you must obtain explicit permission to re-use the figure from the previous publisher (this can be in the form of a letter from an editor or a link to the editorial policies that allows you to re-publish the figure). Please upload the text of the re-print permission (may be copied and pasted from an email/website) as a Word document to the Editorial Manager site in the "Supplemental files (as requested by JoVE)" section. Please also cite the figure appropriately in the figure legend, i.e. "This figure has been modified from [citation]."

Response: We confirm that all figures in the paper are original and have not been previously published.

Comments from Peer-Reviewers:

Reviewer #1:

Manuscript Summary:

Re: # JoVE60300. The authors present a well written and thorough, up-to-date review of current imaging features of Systemic Sclerosis - ILD. It is well worth publishing!

Major Concerns:

2. Protocol: It is understood that the author's intend to present a practical roadmap presumably to non-radiologists. Their emphasis on radiation exposure however is somewhat misleading: current CT scanners provide an array of advanced techniques to significantly lower radiation exposure - to nearly CXR levels. Given the author's concerns - inclusion of these several alternatives should be included - as well as a statement to the effect that while as always there is risk-benefit considerations to imaging utilization - as the authors themselves clearly indicate - the advantages of CT far outweigh potential risks. Perhaps the authors could emphasize this to better effect.

Response: These comments have been addressed in paragraphs one and two of the Discussion.

3. Protocol: the authors paragraph regarding reporting is confusing as noted. Are the author's prepared to suggest a method for standardizing reports for improvement - or at least noting that this is an increasingly popular and accepted approach?

Response: Thank you for your comment. We suggest that this point is removed from the Protocol section, and have marked it for deletion.

4. Diagnosis: the authors should consider including in their description of findings (pg 6 line 143) traction bronchiolectasis as well as bronchiectasis - as they do later in the manuscript. This finding is of increasing importance for diagnosing UIP in particular as outlined by the recent Fleischner guidelines - capable of substituting for lack of definitive honeycombing. This is worth emphasizing.

Response: The text has been reworded as follows: “Indeed traction bronchiectasis **and traction bronchiolectasis** are often the predominant features of SSc-ILD …” to address the comment of the reviewer.

5. Prognosis: the authors include statements regarding quantitative CT methods without actually illustrating any of these currently reported. Perhaps this could be rectified by at least one illustrative case?

Response: As these techniques are currently only used for research purposes, unfortunately we do not have any illustrative cases that we can include.

6. Treatment Response: It is especially interesting that the authors include a case (Fig 7) in which disease progression appears to transform from classic NSIP findings to those of UIP. This evolution has been well described previously - perhaps the author' could comment?

Response: We thank the reviewer for this comment. In this case we do not believe this has transformed to a UIP pattern, since the fibrosis on the second set of images still spare the subpleural lung.

Minor Concerns:

1. Abstract: The authors note that CT is the "definitive" imaging method for diagnosis SSc-ILD. Yet elsewhere they are somewhat less definitive - noting HRCT is "the most sensitive non-invasive means for facilitating disease (p4 4 line 87)- and later in the Discussion- HRCT "arguably the most important information". Perhaps the authors could decide on one descriptive?

Response: The sentence has been reworded to “High-resolution computed tomography (HRCT) of the chest is recognized as **a sensitive imaging method** for diagnosing and assessing SSc-ILD” to address the comment from the reviewer.

Reviewer #2:

Manuscript Summary: An excellent review of the importance of HRCT in SSc-ILD. Makes critical points about HRCT acquisition and interpretation from the Radiologist's perspective, but clearly written so that a radiologist in training or interested non-radiologist physician can follow. Also, very up-to-date information on the topic, particularly with imaging signs and treatment. Figures and tables are well selected, clearly explained and add value to the text.

Major Concerns: None.

Minor Concerns:

In "Representative Results" section, it would be nice to mention/discuss the temporal behavior of SSc-ILD relative to mentioned patterns in this section (transient GGO, evolution from NSIP to UIP...). Then in the "Treatment Response" section, only discuss temporal behavior as it relates to treatment.

Response: Thank you for your comment. We believe that suggesting temporal behavior based on pattern is problematic, which is why we do serial scans. As such we would like this section to remain unchanged.

In "Representative Results" section, may want to mention an upper age limit/range in which a dilated esophagus no longer helps differentiate SSc-ILD and IPF.

Response: Thank you for your comment. Further to your comment, we have included the following text in tracked changes: While there is no accepted upper age limit where a dilated esophagus may no longer help to differentiate SSc-ILD and IPF, a dilated esophagus may be more difficult to interpret in patients over age 65 due to increasing incidence of esophageal motility disorders.

In "Prognosis", might want to describe imaging "prognostic factors" as imaging "biomarkers" as that is becoming a keyword in individualized medicine and quantitative imaging.

Response: Text adjusted as suggested by reviewer.

In "Discussion", might add "...and exclusion of complicating disease such as infectious pneumonia in the setting of acute worsening of symptoms" to the sentence stating the "best use of chest radiographs is to monitor for progressive disease between HRCT scans".

Response: Additional clause added to sentence as suggested by the reviewer.

Editing suggestions- Remove the word 'individuals' from Introduction, paragraph 2, sentence 1.

Response: Text adjusted as suggested by reviewer.

"HRCT" is misspelled in Introduction, paragraph 7, sentence 1.

Response: Text adjusted as suggested by reviewer.

In the Protocol section, the first sentence should not be numbered.

Response: The text of the Protocol section has been rewritten to adhere to journal guidelines.

In the Protocol section, point 7(Justification for expiratory imaging) should be incorporated as a second sentence in point 6.

Response: The two points highlighted by the reviewer have been reformatted as a list of instructions as required by the journal.