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Management of Systemic Sclerosis-Associated Interstitial Lung Disease

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Abstract

Purpose of review—To review the recently published data and provide a practical overview for management of systemic sclerosis-interstitial lung disease (SSc-ILD).

Recent Findings—Published evidence shows considerable practitioner variability in screening patients for ILD. Recent published data supports use of cyclophosphamide or mycophenolate mofetil as first line treatment of SSc-ILD. For patients not responding to first line therapies, consideration is given to rituximab as rescue therapy. Recent trials of hematopoietic autologous stem cell transplantation have demonstrated benefit in patients with progressive SSc-ILD. Anti-fibrotic agents are approved in idiopathic pulmonary fibrosis; studies with anti-fibrotics are underway for SSc-ILD.

Summary—The specter of rapidly progressive lung disease requires clinicians to risk stratify patients according to known predictors for progression and rigorously monitor for symptoms and advancing disease. The above-mentioned therapies promise improved efficacy and favorable side effect profiles compared to cyclophosphamide.

Keywords

Systemic Sclerosis; Interstitial Lung Disease; Management; Treatment

INTRODUCTION

*Systemic Sclerosis-Associated Interstitial Lung Disease*Systemic sclerosis (SSc) is an autoimmune disease that is characterized by immune dysregulation, vasculopathy, and overproduction of collagen leading to skin and internal organ fibrosis[1]. Systemic sclerosis associated interstitial lung disease (SSc-ILD) is a complex process involving inflammation, alveolar epithelial damage, and the activation of resident fibroblasts resulting in thickening

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of the pulmonary interstitium[2]. The reported prevalence varies widely (16-91%) depending on the definition used[3,4]. The prevalence as determined by high-resolution CT (HRCT) ranges from 47-84%[4,5,6]. Patients with diffuse cutaneous SSc are more likely to develop SSc-ILD (53%) compared to those with limited cutaneous SSc (35%)[7]. SSc-ILD has become the leading cause of death (alongside pulmonary arterial hypertension) and accounts for up to 30-35% of SSc mortality[8,9]. SSc-ILD has heterogeneous disease progression: many patients will have a chronic, indolent course while others may develop progressive, life-threatening disease. Symptoms of cough and exertional dyspnea may be absent or mild early in the disease course. Universal screening is paramount in identifying these patients early. Not all patients require treatment if the disease is detected; monitoring for progression is an essential component of disease management.

Several risk factors for progressive SSc-ILD have been identified (Table 1) and prognostic scoring systems have identified predictors of mortality[5,10,11]. Considerable variation exists among rheumatologists and SSc experts in terms of practice patterns for SSc-ILD screening and treatment[12,13]. This article reviews the current literature in terms of screening and treatment recommendations and provides our treatment algorithms for SSc-ILD patients.

DISEASE SCREENING AND MONITORING

All patients with SSc should be screened for ILD.

The variable nature of SSc-ILD and lack of robust predictive markers or prediction models makes it challenging to assess who will develop clinically meaningful disease. Although low-risk populations have been identified (e.g., those with anti-centromere antibodies), considerable variability in risk for progression exist[2]. With the advent of increasingly efficacious treatment with improved toxicity profiles, we recommend that all patients with SSc should be screened with pulmonary function tests (PFTs) and high-resolution chest CT (HRCT) for ILD.

Despite this, a recent global survey[13] showed that a wide variability exists in rheumatologists' use of HRCT in screening practices: only half of general rheumatologists and two-thirds of SSc experts routinely obtain a chest HRCT in newly diagnosed SSc patients. Between the two groups, there were no 100% agreed-upon indications for which an HRCT should be performed (e.g., respiratory symptoms, physical exam finding, oxygen desaturation, or PFT deficit).

Screening and Monitoring.

Screening should involve a careful review of systems, physical examination, complete PFTs with lung volumes, and lung imaging with HRCT (with prone images, see Figure 3)[14], and may include functional measures like the 6-minute walk test[15] (See Figure 1). Echocardiography and use of the DETECT algorithm should be performed at baseline to exclude concurrent pulmonary hypertension[16,17].

Once the diagnosis of SSc-ILD is established, it is important for the treating clinician to identify the constellation of factors that designate one patient to receive routine monitoring

(as their risk for progressive ILD may be low), and for another patient to initiate or escalate immunomodulatory treatment (as risk for progressive ILD is high; Table 1)[18,19].

HRCT.

HRCT is the only non-invasive way to diagnose ILD. It can characterize the nature and extent of lung involvement. The majority of cases are fibrotic NSIP pattern (figure 4), with a minority (10-15%) with UIP pattern (figure 5); the mortality rates between these two disease patterns do not differ significantly in SSc-ILD[20].

Quantifying the extent of fibrosis has yielded important information including prediction of pulmonary function decline[21] and risk for mortality[5,22,23,24]. Advances in quantitative measurements of fibrosis[25] has allowed HRCT to become a valuable tool for detecting response to treatment. Kim et al., 2016[26] showed that patients treated with cyclophosphamide in the Scleroderma Lung Study-I had decreasing extents of fibrosis, suggesting quantitative HRCT is a sensitive measure for assessing treatment response. Goldin et al., 2018[27] also found significant reductions in the extent of fibrosis in response to treatment in the Scleroderma Lung Study-II, which correlated with improving FVC, DLco, and breathlessness.

In clinical practice, we recommend volumetric HRCT with supine and prone images in all patients with SSc. Repeat HRCT should not be routinely performed but considered in patients with progressive symptoms attributable to ILD if it will direct treatment decisions, or in clinically stable patients with declining PFTs to assess for radiographic progression.

Radiation dose from medical imaging has been a growing concern with patients getting scanned repetitively for diagnosis and follow up. For perspective and comparison, the typical effective dose from natural background radiation in North America is 3 millisievert (mSV)[28]. The effective dose of a PA and lateral radiograph is 0.05 mSV. The effective dose to a 70 kg adult for a chest CT is approximately 5.4 mSV[29], and the dose can vary depending on BMI and protocol (HRCT would be more if expiratory and prone imaging are also performed as dose from each would be additive). CT protocols have been tweaked over the last decade in an attempt to reduce radiation exposure with use of tube current modulation, reduced tube voltage, higher pitch and noise reduction filters[30]. Typically attempts at dose reduction are accompanied with increased image noise which results in decreased spatial resolution and impairment of the ability to see subtle interstitial abnormalities. Lim et al., 2016[30] demonstrated that types of iterative reconstruction (a newer image reconstruction technique) have been successfully used to decrease image noise in low dose HRCT studies achieving radiation doses around 0.7 mSV versus 3.1 mSV for annual background radiation. However, they noted that these reconstruction techniques tended to overestimate ground glass opacity and underestimate interlobular septal thickening. Dose reduction in HRCT with iterative reconstruction has a lot of potential with larger trials being necessary before it is adopted more widely.

PFTs.

Pulmonary function tests represent a cost-effective, clinically feasible, safe and reliable means of early detection of SSc-ILD. The broad range of PFTs considered normal

(80-120%) can make interpretation of a cross-sectional evaluation difficult during the first visit. PFTs lack sensitivity and specificity (relative to HRCT) in early or mild disease[3], making PFTs more apt for disease monitoring than screening. Baseline FVC abnormalities have been shown to predict mortality at 10 years from disease onset[31,32]. Patients who reach an FVC of 50-70% of the predicted value within 5 years of onset of disease has been associated with end-stage ILD and increased mortality[31,33]. As a result, PFTs are routinely performed every 3-6 months for the first 3-5 years of disease[34]. Goh et al., 2017[35] found that change in FVC and DLco was predictive of mortality at 1 year (in those with extensive disease); at 2 years, DLco and Kco trends had the greatest prognostic significance. Volkmann et al., 2018[36] examined patients in SLS-I and SLS-II for significant predictors of long-term mortality and found that the course of FVC and DLCO over 24 months appeared to predict long-term survival better than the baseline measurements of these parameters. This further emphasizes the need for early identification and regular PFTs in early disease.

Our Screening and Monitoring Algorithm

All patients should be evaluated for pulmonary hypertension contemporaneously with ILD screening and prior to pursing ILD treatment. Figure 1 is a proposed screening algorithm for clinical SSc-ILD and for monitoring those with subclinical SSc-ILD or no evidence of ILD at the time of screening. For patients with clinical SSc-ILD (mild-to-severe ILD on HRCT, persisting PFT deficits, and in whom symptoms are attributable to ILD), we initiate treatment. We consider treatment on a case-by-case basis for those who have subclinical ILD with high risk features, including asymptomatic patients with mild ILD on HRCT, mild PFT deficits, and early dcSSc status with high risk biomarkers like a positive anti-SCL 70 antibody[33,37] or elevated CRP[38,39]. In patients without ILD on HRCT we proceed with routine monitoring with PFTs; the development of ILD on HRCT or mild-to-severe deficits on PFTs prompts consideration for treatment.

Figure 2 is a proposed screening algorithm for patients with SSc-ILD who develop worsening respiratory symptoms. Routine and transient causes of cough or mild dyspnea should be considered and excluded (e.g., viral upper respiratory infection, asthma, allergic rhinitis with post nasal drip syndrome, GERD). Sustained or disproportionate decline in DLco prompts simultaneous consideration for development of PAH. We obtain a repeat echocardiogram, serum NT-pro BNP, serum uric acid and calculate DETECT scores to assess if there is developing/advancing pulmonary hypertension, based on 2018 recommendations from the World Pulmonary Hypertension Symposium[40,17]. Patients should also be assessed for pulmonary and non-pulmonary etiologies for restrictive lung disease, including reduction in chest wall compliance, possible diaphragmatic weakness, deconditioning, and concurrent myopathy. If these measures cannot account for symptoms or changes in PFTs, we repeat HRCT to assess for progressive ILD.

DISEASE TREATMENT

Who Requires Treatment

All patients with clinically meaningful SSc-ILD should be offered treatment. Although no consensus definition exists, clinical ILD may be defined as those patients with symptoms

attributable to ILD and non-trivial lung involvement seen on HRCT and/or associated decrements in lung physiology and gas exchange[41]. Disease monitoring should be rigorous in order to detect the subset of clinical ILD patients with progressive disease, operationalized as a decline in FVC levels of >10% from baseline or ≥ 5% to < 10% relative decline in FVC and ≥ 15% relative decline in DLCO[42,43] although smaller changes may be clinically meaningful, especially worsening symptoms attributable to ILD[43]. These patients span a spectrum from mild to rapidly progressive disease, with the latter often having cardinal clues to their risk of progression (e.g., larger extent of fibrosis on HRCT at baseline, shorter duration of SSc, high CRP; see Table 1)[44]. Decisions to initiate or advance treatment often take into consideration the likelihood of progression, patient comorbidities, risk of toxicities, and current data on efficacy.

Treatment Options

The goal of treating clinical SSc-ILD stabilization or preventing progressive disease[45].

Cytotoxic DMARDs

Scleroderma Lung Study I (1-year course of oral cyclophosphamide (CYC) up to 2 mg/kg/day) showed a statistically significant but small improvement in FVC (2.5% improvement) vs. placebo and a paucity of sustained benefit after the medication was discontinued. Scleroderma Lung Study II (head-to-head comparison of oral CYC up to 2 mg/kg/day for 1 year to mycophenolate mofetil (MMF) at 1.5 grams twice a day for 2 years) showed MMF to have a positive treatment effect on FVC similar to those treated with oral CYC at 2 years (MMF 2.2%, CYC 2.9%), improved measures of dyspnea, and MMF had a superior safety profile.

Biologic DMARDs

Phase III clinical data suggest the role of the IL-6 pathway in SSc-ILD and treatment of early SSc with elevated CRP led to stabilization of FVC% in tocilizumab group vs. a clinically meaningful decline in the placebo group over 48 weeks: treatment difference of 4.2%; $p = 0.0002$. The mean [SD] FVC% was 82.1% [14.8%] at baseline and this trial highlights the benefit of treating patients with subclinical ILD with high risk features (early dcSSc, and elevated CRP) [39], further emphasizing the need for early detection of the disease.

Rituximab (RTX) therapy in SSc has gained favor in response to promising effects on both ILD and skin thickening. A recent open-label, randomized, controlled trial of head-to-head RTX vs. monthly pulse CYC analyzed a population of 60 early, treatment naïve, anti-SCL-70+, dcSSc with ILD patients receiving either arm. Patients in the CYC group received 500mg/m^2 CYC IV pulses every 4 weeks for 24 weeks; patients in the RTX group received two RTX pulses of 1000mg at 0 and 15 days. They found the RTX group to have improved FVC% at the end of 6 months (RTX group improved, 61.3% to 67.5% while the CYC group did not, 59.3% to 58.1%). The efficacy and safety demonstrated in this trial argues that RTX may be considered as a first line therapy.

Autologous Hematopoietic Stem Cell Transplant

Hematopoietic stem cell transplant (HSCT) represents an emerging treatment option for those patients with SSc-ILD that is severe and refractory to standard therapy, and who are likely to benefit from the procedure while unlikely to develop post-transplant complications. Three key trials (ASSIST, ASTIS, and SCOT) have shown improved survival compared to CYC, in addition to improved quality of life, skin thickening, and FVC[46]. Due to limited space, we will only discuss the recently published SCOT trial[47].

SCOT was a multi-center randomized phase III trial including 75 patients with early dcSSc; 100% of patients in the HSCT group had ILD. HSCT patients (n= 36) were conditioned with CYC (120mg/kg), anti-thymocyte globulin, received total body irradiation (800cGy) and received a stem cell transplant (CD34+ selected); the comparator arm received CYC (750mg/m^2) x12 months (n= 39). At baseline, the two groups had similar averages [SD] on FVC: 74.5% [14.8] in the HSCT group compared to 73.8 [17.0] in the CYC group. The two groups also had similar averages on DLco: 53.9% [7.6] compared to 52.7 [8.2], respectively.

Overall, the trial demonstrated that HSCT significantly improved event-free survival compared with CYC, where ‘event-free’ was operationalized as survival without respiratory, renal, or cardiac failure. With specific focus on SSc-ILD and respiratory outcomes, more patients receiving HSCT improved in FVC than those in the CYC group at 54 months: 36% of the HSCT patients improved (relative increase of FVC by ≥10%) compared to 23% of the CYC patients. Conversely, fewer patients in the HSCT group worsened (relative decrease by ≥10%) compared to the CYC group (17% vs. 41%, respectively). HSCT was also associated with improvement on the HRCT compared to CYC on computer-based quantitative image analysis[48].

Lung Transplant

Lung Transplant remains a therapy for appropriately selected candidates with treatment-refractory lung disease[49]. Advancing disease should prompt an early referral, as these patients require a multi-disciplinary evaluation prior to transplant consideration and optimization prior to procedure. One nationwide cohort study found an increased 1-year mortality rate in SSc-ILD patients compared to those with non-SSc-ILD[50]. Outcomes of mortality up to 5 years suggest similar outcomes to those with non-SSc fibrotic lung disease[51].

Our Treatment Practice

In clinical SSc-ILD, we initiate induction therapy using MMF with a goal of 3 grams/day in divided dose. If not tolerated, we ensure the patient is taking MMF with food as this may decrease nausea/vomiting. If intolerance remains, we recommend comparable dosing for mycophenolic acid (720mg three times daily). In clinical SSc-ILD patients with rapidly progressive disease or those with significant GI dysmotility, we advance to pulse monthly CYC at 500-750 mg/m^2. For those not responding, we consider the addition of RTX 1000 mg for 2 doses. In patients with early dcSSc and progressive ILD (on PFT, HRCT, and/or symptoms), who are not responding to MMF or other immunosuppressive therapy, we

consider HSCT[52]. Based on recent data[53], we now consider tocilizumab as first line therapy in early dcSSc and subclinical ILD.

Non-pharmacologic Therapy

All patients with SSc-ILD should have a multidisciplinary team. Comorbid gastrointestinal disease, especially GERD and aspiration should be considered. Every SSc-ILD patient should be educated to sleep at an angle and aggressively control ongoing GERD symptoms. All patients with SSc and especially those with SSc-ILD should be encouraged to quit smoking and tobacco products. Supplemental oxygen should be provided to those patients requiring it to maintain SpO2 ≥88% during ambulation. All patients should be given inactive influenza and pneumococcal vaccines, administered before starting B cell depleting biological therapy[54]. Finally, pulmonary rehabilitation [55] may be effective. For those patients who may be considered a transplant candidate, pulmonary rehabilitation will be a necessary step in their evaluation.

FUTURE DIRECTIONS

Emerging Therapies

Idiopathic pulmonary fibrosis is a fibrotic lung condition which shares pathological features with SSc-ILD of fibroblast proliferation, migration, and differentiation[56]. Nintedanib is an intracellular tyrosine kinase inhibitor approved for the treatment of IPF and is currently being investigated in a phase III, multicenter, double-blind, placebo-controlled trial (SENSCIS;)[57]. The final results are anticipated in 2019.

The LOTUSS trial[58] was a phase II international, multicenter, open-label assessment of Pirfenidone, an anti-fibrotic/anti-inflammatory agent also approved for IPF. This study showed tolerability and safety with concurrent use of MMF. The Scleroderma Lung Study-III is an on-going trial since 11/2017 comparing MMF and pirfenidone vs. MMF and placebo (). The goal enrollment is 150 patients with SSc-ILD and the primary endpoint is FVC at 18 months. There are several other ongoing clinical trials for SSc-ILD[59].

CONCLUSION

ILD is common in SSc. At present we lack the granularity in predicting which subsets of patients will develop organ and potentially life-threatening disease. The potential risk for morbidity and mortality is the impetus for rigorous monitoring for symptoms and signs of ILD development and progression. At this time, the standards of care include cyclophosphamide and mycophenolate mofetil, both of which have shown modest improvements in FVC; treatment supports the attenuation of disease progression. Newer therapies include biologics, stem cell transplant, and anti-fibrotics; preliminary data suggest improved efficacy and safety profiles compared to cyclophosphamide therapy.

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Key Points

- Point 1

  Diagnosis of SSc-ILD is determined by HRCT; prognosis depends on a constellation of risk for progressive SSc-ILD (disease type, auto-antibody status, extent of involvement on HRCT, pulmonary function impairment).

- Point 2

  There is a large disparity in screening practices by rheumatologists in terms of who gets screened for ILD.

- Point 3

  Not all patients with SSc-ILD require treatment. Patients should be routinely monitored earlier in the disease. Early and aggressive treatment with non-pharmacologic and pharmacologic therapies are warranted.

- Point 4

  Anti-fibrotic agents and repositioned biologic therapies are currently being studied in clinical trials for SSc-ILD.

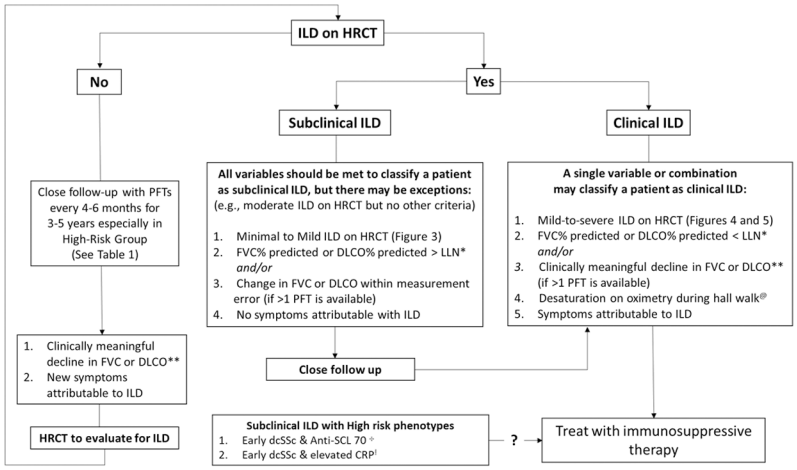

Figure 1: Screening and Monitoring Algorithm for ILD in Patients with SSc

* Lower limit of normal

** Clinically meaningful decline defined as FVC levels of >10% from baseline or decline in FVC ≥ 5% to < 10% and ≥ 15% relative decline in DLCO

@ Other causes of desaturation such as pulmonary hypertension should be ruled out

+ Based on Sircar et al., 2018[37]

! Based on Khanna et al., 2016[39,53]

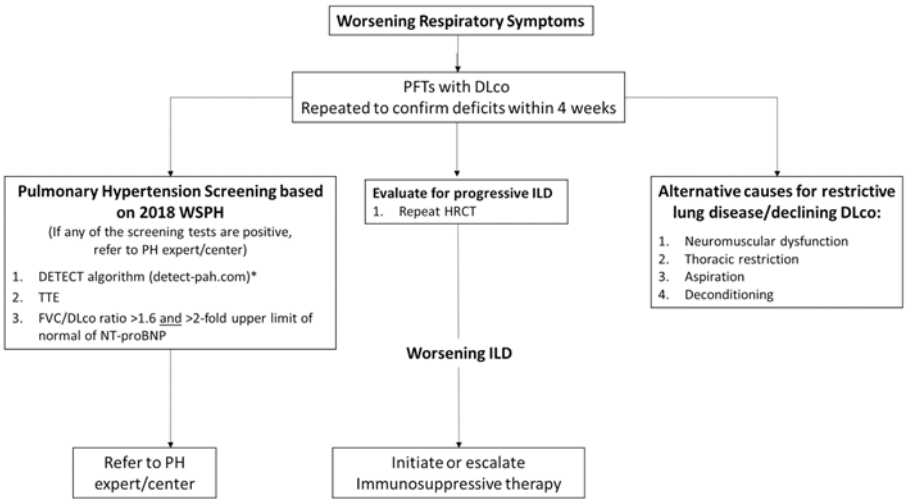

Figure 2: Work-up for SSc-ILD Patients with Worsening Respiratory Symptoms

* Based on Coghlan et al., 2015[16]

WSPH World Symposium on Pulmonary Hypertension[17]

PH Pulmonary Hypertension

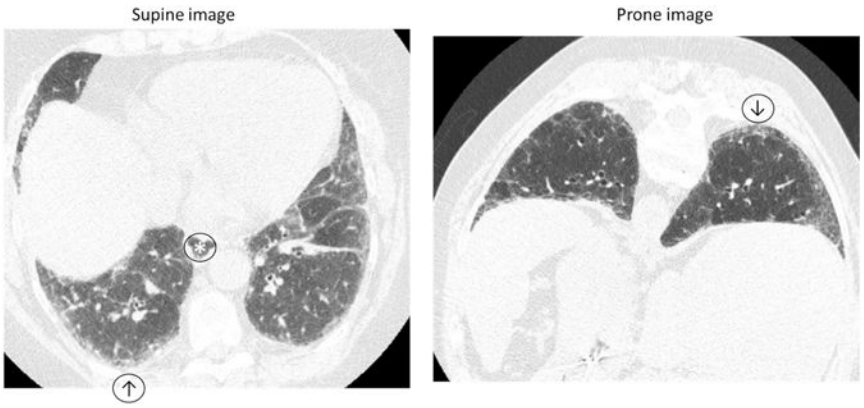

Figure 3: HRCT in SSc-ILD

Inspiratory and prone HRCT demonstrating minimal reticulation, subpleural groundglass opacity (↑) that persists on prone imaging (↓) suggestive of interstitial lung abnormalities and an early fibrotic lung disease. No honeycombing or traction bronchiectasis. Note slightly dilated esophagus (*).

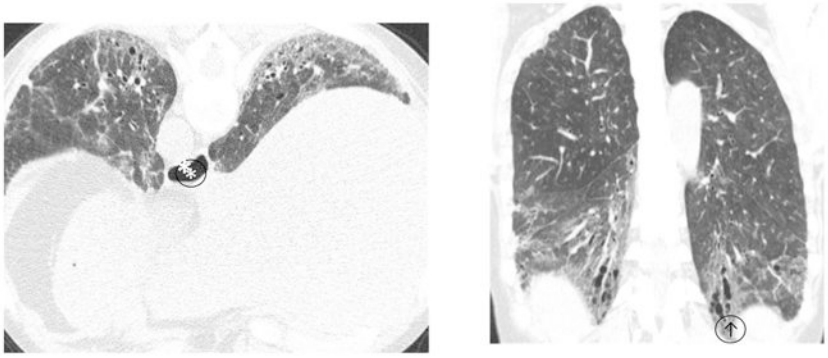

Figure 4: Non-Specific Interstitial Pneumonitis Pattern

Lower lung predominant homogeneously distributed ground glass opacity, reticulation, traction bronchiectasis(↑) and dilated esophagus (*)without honeycombing. Appearances are compatible with scleroderma related interstitial lung disease (NSIP pattern).

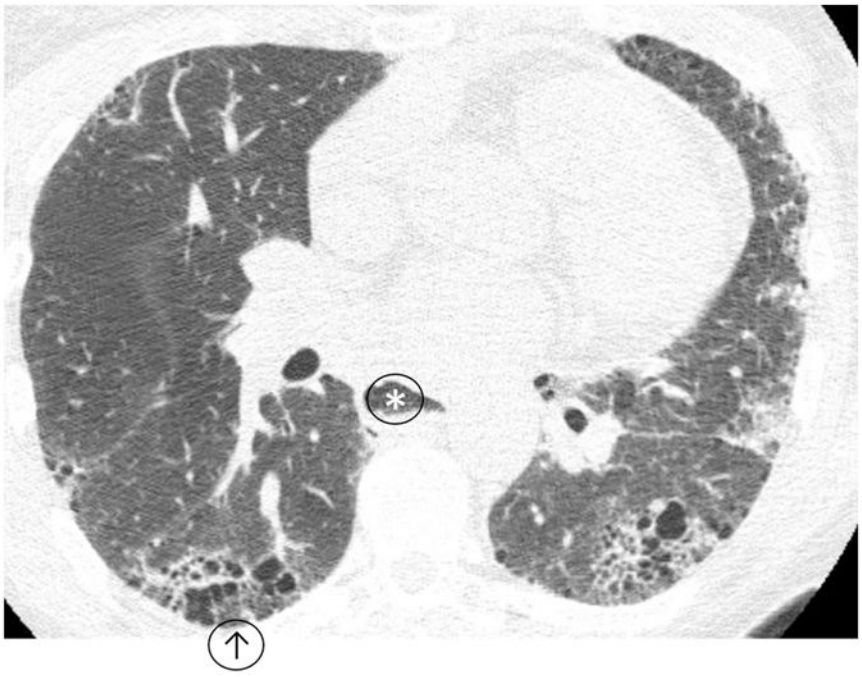

Figure 5: Usual Interstitial Pneumonitis Pattern

Heterogeneously distributed interstitial lung disease with honeycombing (↑) compatible with usual interstitial pneumonitis due to scleroderma, note dilated esophagus (*).

Table 1:

Features predictive of disease progression in SSc-ILD.

FEATURE	Reference
DEMOGRAPHIC	
Male gender	60
African-American race	61
DISEASE STATUS	
Diffuse cutaneous systemic sclerosis	33
BIOMARKERS	
Anti-SCL 70 Ab	33
Nucleolar pattern on ANA (representing anti-Th/To, U3 RNP)	62
CCL-2	64
CCL-18	64
Interleukin-6	65
C-reactive protein	38
CXCL-4	66
KL-6	67
Surfactant protein D	68
PULMONARY FUNCTION TESTING	
Baseline FVC <70%	69
Baseline DLco <55%	33
IMAGING	
HRCT fibrosis >20%-25%	21,22
HRCT total lung involvement >20%	5, 21