ILD Collaborative

Project ECHO

Scleroderma-associated ILD: Clinical manifestations and diagnosis

Robert Hallowell, MD

Disclosures

- Speaking and consulting fees: Boehringer Ingelheim, Genentech
- Research trials: Boehringer, Genentech, Galapagos, Hoffmann-La Roche, Nitto Denko, Vicore
- Authorship fees: UpToDate, Dynamed

Scleroderma or Systemic Sclerosis (SSc)

Autoimmune disease characterized by systemic inflammatory, fibrotic, and vasculopathic changes

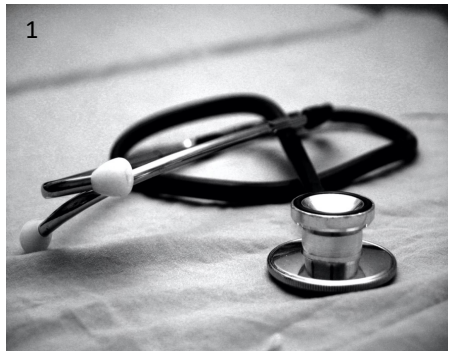
Divided into three primary subsets:

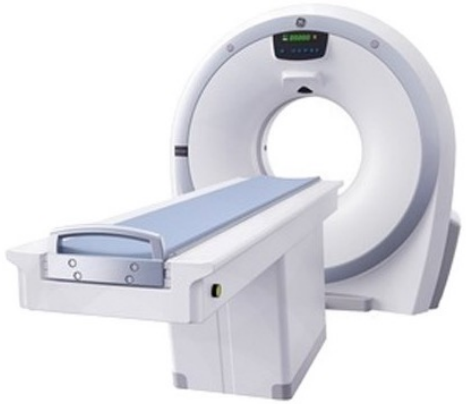
- Limited cutaneous (Skin changes are distal to the elbows and knees; face and neck involvement)
  - CREST (**C**alcinosis, **R**aynaud's, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasias)
- Diffuse cutaneous (Skin changes extend to or beyond the elbows and knees)
- Systemic sclerosis sine scleroderma (No skin thickening; internal involvement and positive antibodies)

We see significant pulmonary involvement with all three subsets of SSc!

Rheumatologist
Does my SSc patient have ILD?

1

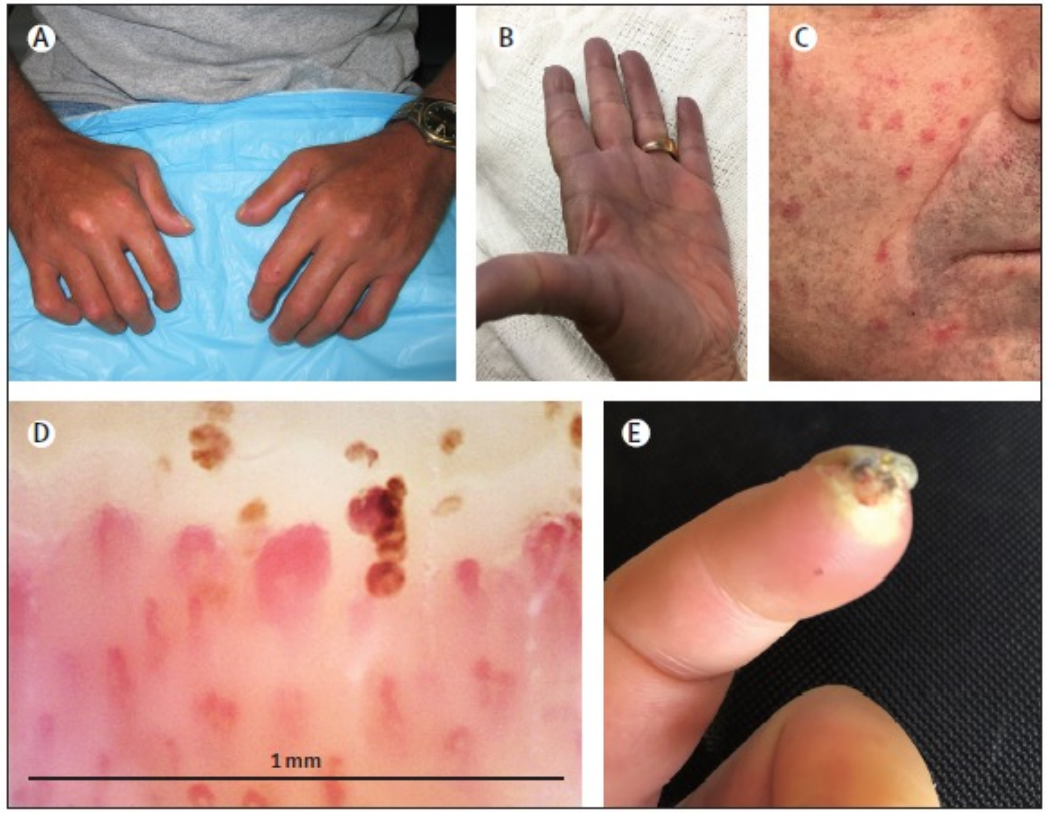




High risk serologies

Pulmonologist
Does my ILD patient have SSc?

2



Symptom review

Exam

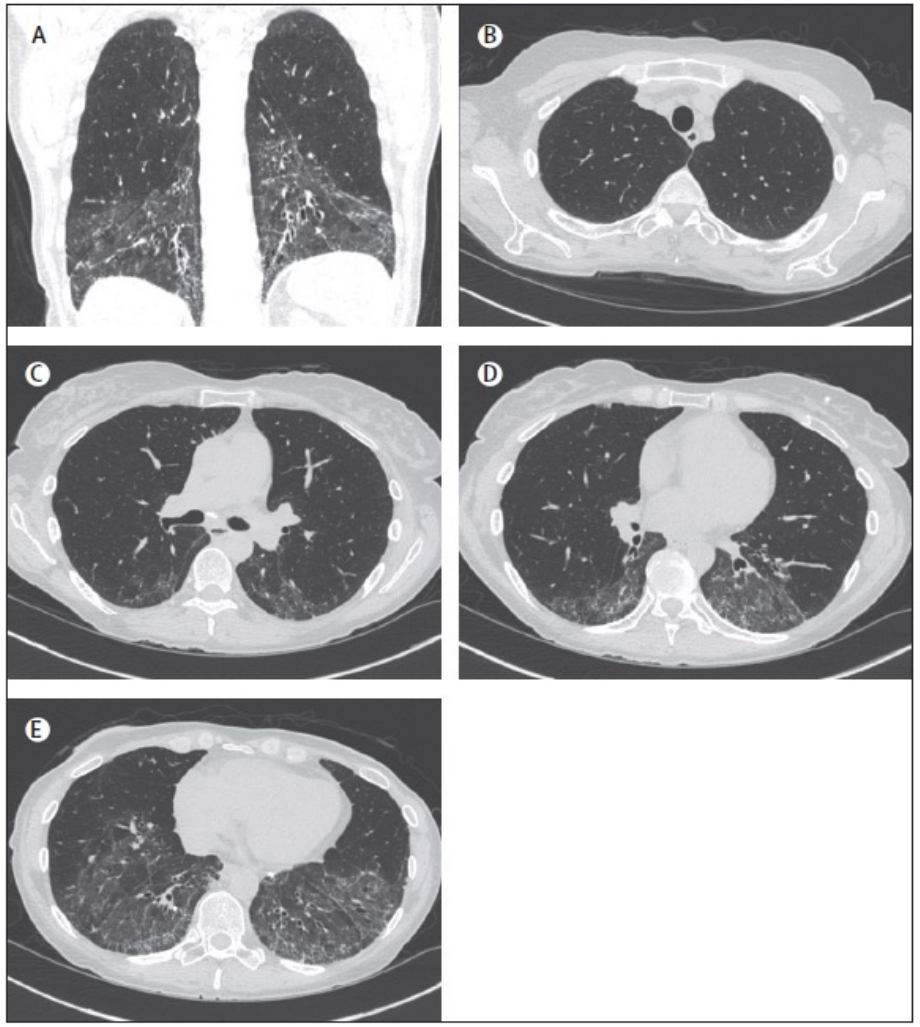
Serologies

1. Hush Naidoo Jade images

2. Perelas et al. *Lancet Respir Med* 2020;8: 304–20

ILD is common in SSc

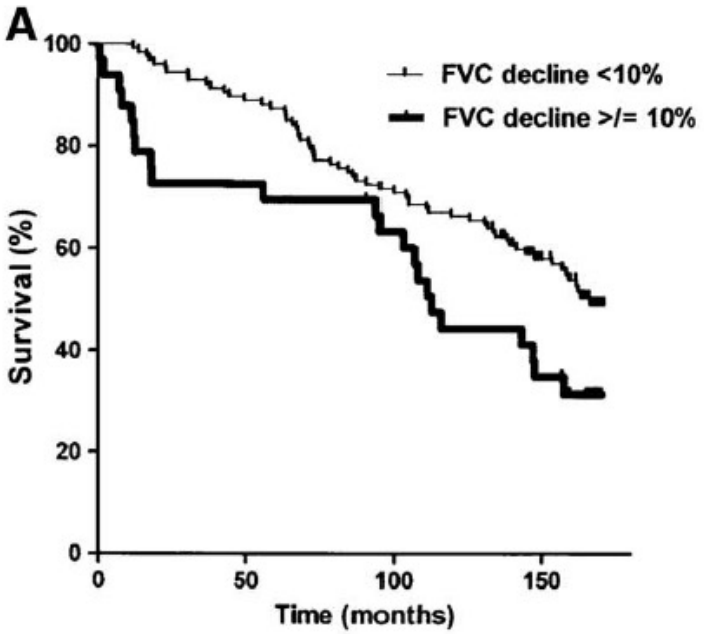
- Seen on CT in up to 80% patients
- Seen on autopsy in up to 90% of patients
- Clinically significant in 30-40% of patients
- 10-year mortality of SSc-ILD up to 40%



Perelas et al. *Lancet Respir Med* 2020;8: 304–20

ILD is associated with death in SSc

- 162 patients with SSc-ILD
- 12-month PFT trends on 15-year survival
- HR 1.84, p = 0.01



Goh et al. *Arthr & Rheum* Vol. 69, No. 8, Aug 2017, pp 1670–1678

- 5860 SSc patients in the EULAR trials and EUSTAR cohort
- Cause of death analyzed for 234/284 cases
- 33% of deaths attributed to a pulmonary cause; 19% pulmonary fibrosis

Table 1 Primary causes of death in 234 patients with SSc

	N	%
All death cases	234	100
SSc-related death cases	128	55
Pulmonary	78	33
Pulmonary fibrosis	45	19
Isolated PAH	33	14
Myocardial	33	14
Arrhythmia	14	6
Left heart failure	8	3
Right heart failure	5	2
Biventricular heart failure	4	2
Pericarditis (constriction and/or tamponade)	2	1
Renal	10	4
Renal crisis	10	4
Gastrointestinal	7	3

Tyndall et al. *Ann Rheum Dis* 2010;69:1809–1815.

Diagnosing Scleroderma--ACR/EULAR Criteria

Items	Sub-items	Score
Bilateral skin thickening of the fingers		9
	Puffy fingers	2
	Sclerodactyly	4
Fingertip lesions	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasias		2
Abnormal nailfold capillaries		2
PAH (RHC) or ILD		1-2
Scleroderma related Antibodies	Anti-Centromere Anti-Topoisomerase 1 Anti-polymerase III	1-3

9 points = definite SSc

Sensitivity 91%
Specificity 92%

Van den Hoogen et al. *Arthritis Rheum*. 2013 November ; 65(11): 2737–2747.

Autoantibodies in SSc

	Antibody	Frequency in SSc	Disease Subtype	Clinical Association
*	**Anti-Topoisomerase 1 (Scl-70)**	**15% - 42%**	**dc-SSc**	**ILD**
*	**Anti-Centromere**	**20% - 38%**	**lc-SSc**	**PAH**
	Anti-Th/To	**1% - 13%**	**lc-SSc**	**ILD**
*	Anti-RNA-polymerase III	5% - 31%	dc-SSc	Renal crisis, synovitis, myositis, tendon friction rubs, malignancy
	Anti-U3-RNP	4%-10%	dc-SSc	Renal crisis, cardiac involvment
	Anti-U1-RNP	2%-14%	lc-SSc	Raynaud's, puffy fingers, arthritis, myositis, MCTD
	Anti-PM-Scl	**4%-11%**	**lc-SSc**	**ILD, myositis, sicca, calcinosis, arthritis**
	Anti-Ku	2%-4%	--	Myositis, arthritis, joint contractures

Adapted from Kayser C, et al. *Front Immunol*. 2015;6:167.

Panel 1: Factors associated with the presence of systemic sclerosis-associated interstitial lung disease

Epidemiology
- African American race
- Male sex
- Genetic polymorphisms

Clinical features
- Diffuse cutaneous scleroderma variant
- Nailfold capillary abnormalities
- Digital ulcers
- Longer disease duration
- Pulmonary hypertension

Autoantibodies
- Anti-topoisomerase I
- Anti-neutrophil cytoplasmic antibody
- Anticardiolipin
- Anti-Ro52
- Anti-NOR90
- Anti-U11/U12
- Anti-Th/To
- Anti-polymyositis-scleroderma

Novel Biomarkers
- Interleukin-6, interleukin-34
- chemokine (C-X-C motif) ligand 4
- chemokine (C-C motif) ligand 18
- Carbohydrate antigen 15·3
- Lysyl oxidase
- Tenascin-C
- Serum amyloid A
- Surfactant protein D
- Chitinase 1
- Krebs von den Lungen-6
- Cartilage oligomeric matrix protein

ILD progression

Panel 2: Risk factors for systemic sclerosis-associated interstitial lung disease progression

Epidemiology
- Male sex
- Active smoker
- Older age at presentation

Clinical features
- Digital ulcers
- Arthritis
- Increased oesophageal diameter
- Pulmonary hypertension
- Progressive skin fibrosis
- Renal disease
- Myocardial fibrosis

Physiology and imaging
- Forced vital capacity (FVC) decrease of more than 10%
- More than 20% fibrosis on high-resolution CT
- Pulmonary artery-to-aorta ratio of more than 1:1
- FVC decrease of 5–9% with decrease in diffusing capacity for carbon monoxide of more than 15%
- Usual interstitial pneumonia pattern

Novel Biomarkers
- Fractional excretion of nitric oxide
- Interleukin 10
- Carbohydrate antigen 15·3
- C-reactive protein
- Monocyte chemoattractant protein 1

PFTs are a poor screening tool for ILD in patients with SSc

Retrospective study of 212 patients
All had received CT imaging and PFTs in the **P**rospective **R**egistry of **E**arly **S**ystemic **S**clerosis (**PRESS**; 11 sites)
54% had radiographic ILD

Performance Characteristics of Pulmonary Function Tests for the Detection of Interstitial Lung Disease

PFT Parameters	N	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR	FPR	FNR
FVC < 80%	212	63%	68%	70%	61%	2.0	0.5	0.32	0.37
TLC < 80%	146	46%	77%	74%	51%	2.0	0.7	0.23	0.54
DLCO < 80%	200	80%	51%	66%	68%	1.6	0.4	0.49	0.20
FVC or DLCO < 80%	199	85%	42%	64%	70%	1.5	0.4	0.58	0.15
FVC or TLC or DLCO < 80%	143	85%	42%	68%	66%	1.5	0.4	0.58	0.15

ILD patterns in SSc-ILD

Section G: Baseline characteristics (SENSCIS trial-576 patients)

Characteristic	Nintedanib (n=288)	Placebo (n=288)
Female – no. (%)	221 (76.7)	212 (73.6)
Age – yr	54.6±11.8	53.4±12.6
Body mass index – kg/m^2	25.9±4.8	25.8±5.1
Race – no. (%)†		
White	201 (69.8)	186 (64.6)
Asian	62 (21.5)	81 (28.1)
Black/African-American	20 (6.9)	16 (5.6)
American Indian/Alaska Native/Native Hawaiian/other Pacific Islander	3 (1.0)	3 (1.0)
Diffuse cutaneous SSc – no. (%)	153 (53.1)	146 (50.7)
Years since onset of first non-Raynaud symptom – median (minimum, maximum)	3.4 (0.3, 7.1)	3.5 (0.4, 7.2)
Extent of fibrosis on HRCT – %	36.8±21.8	35.2±20.7
Honeycombing on HRCT – no. (%)	44 (15.3)	45 (15.6)
Reticulation on HRCT – no. (%)	266 (92.4)	272 (94.4)
Ground glass opacities on HRCT – no. (%)	241 (83.7)	246 (85.4)
FVC		
ml	2459±736	2541±816
% of predicted value	72.4±16.8	72.7±16.6
DL_{CO} – % of predicted value‡	52.9±15.1	53.2±15.1
Anti-topoisomerase antibody positive§ – no. (%)	173 (60.1)	177 (61.5)

Retrospective study of 27 SSc-ILD patients undergoing Bx

- **51.9% NSIP pattern**
- **29.6% UIP pattern**
- **18.5% miscellaneous non-ILD pattern**

All patients had limited skin involvement

UIP pattern had a trend towards worse survival

Distler et al. *N Engl J Med* 2019;380:2518-28.

Fischer et al. *Chest* 2008 Sep;134(3):601-605.

Pulmonary Hypertension in SSc patients

Estimated prevalence ranges from 8-15%

WHO group 1 (PAH)—most common
WHO group 2 (Due to left heart disease)
WHO group 3 (Lung disease or hypoxia)

Increases morbidity and mortality

- Annual screening with a TTE
- Low threshold to repeat TTE or refer for RHC
  - Dyspnea out of proportion to CT changes
  - DLCO disproportionately low/declining
  - Concerning exam findings (edema, RV heave)

Summary

- ILD is a common complication of SSc
- ILD is associated with significant morbidity and mortality
- Rheumatologists and pulmonologists need to have an index of suspicion for the presence of ILD and SSc in their respective patient populations
- SSc patients should be carefully screened for the presence of PH