Autoimmune Disease-Associated ILD

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Off label uses of medications described

Take home points

- Autoimmune - specifically connective tissue diseases- commonly lead to ILD
- Ideally pulmonary and rheumatology experts work closely together to diagnose and treat
- Knowing there is an underlying CTD may change treatment
  - Might add anti-inflammatory/immune suppressing medications
  - Might still use anti-fibrotic medication as in IPF

What is an autoimmune disease?

- Body's immune system targets a part of the body and causes damage
- Diagnosis can be complicated
  - Set of specific symptoms
  - Blood tests showing specific antibodies
- Many examples targeting different body parts
  - Celiac disease, Type I diabetes, hypothyroidism

- Introduction to autoimmune and connective tissue diseases (CTDs)
- Guide to workup of CTDs
- Overview of treatments
  - history, physical, labs, radiology
- Details of some specific CTDs

Autoimmune diseases with ILD

- ANCA Associated Vasculitis
  - Associated with antibodies to
  - Inflammation of specific blood vessels
  - Pulmonary fibrosis may also be seen
- "Connective Tissue Diseases" are majority of autoimmune ILD
- Typically seen by "rheumatologists" first
  - From Greek word for "rheuma" - flow
  - Rheum was medieval English term for watery mucus
  - Thought to accumulate in joints and cause swelling

Connective Tissue Diseases

- Over 200 diseases targeting the tissue that holds the body together
- ILD dominant in:
  - Rheumatoid arthritis, Systemic Sclerosis, autoimmune myositis (polymyositis, dermatomyositis)
- ILD seen in:
  - Systemic Lupus Erythematosus (“lupus”; “SLE) Sjögren’s Syndrome, and Mixed Connective Tissue Disease (MCTD)

Why do we look for underlying CTD?

- Prognosis
  - Many studies suggest CTD-ILD has better survival
- Treatment
  - Anti-fibrotic medication (nintedanib) approved for all progressive pulmonary fibrosis
  - Won't treat autoimmune inflammation
  - Treatment may be needed for other manifestations of CTD
- Research
  - Need to define patient populations to understand ILD

Strand et al *Chest* 2014, Park et al. *AJRCCM* 2007 Song et al. *Chest* 2009
Navaratnam et al. *Respiratory J* 2011 Kocheril et al. *ACR* 2005 Kim et al. *ERJ* 2010

Ways to look for CTD

History

Physical Exam

Radiology

Pathology

Strek et al. *Chest* 2013, Fischer & du Bois *Lancet* 2012, Vij et al. *Chest* 2011

Patient history

Occupational or environmental exposures
Fevers, night sweats, weight loss
Muscle weakness
Joint pain or swelling (arthalgia, arthritis)
Dry eyes, mouth (“Sicca symptoms”)
Difficulty swallowing (“Dysphagia)
Reflux/ heartburn (“GERD”)
Rashes – face, chest, hands
Raynaud’s syndrome

Strek et al. *Chest* 2013, Fischer & du Bois *Lancet* 2012, Vij et al. *Chest* 2011

Physical Exam findings

Ambulatory oxygenation

Rashes, oral ulcers

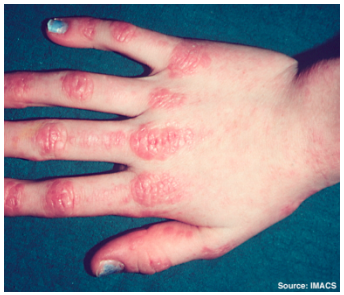
Proximal muscle weakness

Mechanic's hands, Gottron's papules,

Sclerodactyly, digital ulcers

Puffy fingers

Synovitis



Rheumatology consultation can be very helpful

Strek et al. *Chest* 2013, Fischer et al *Chest* 2010, Vij et al. *Chest* 2011, Mittoo et al. *Respir Med* 2009, Castelino et al. *Rheumatology* 2010, Danoff & Casciola-Rosen *Arthritis Res Ther* 2011, Minier et al. *Ann Rheum Dis*. 2013 clinical trial NCT01809574, wikipedia

Radiology of CTD-ILD

Many possible patterns

UIP: Usual Interstitial Pneumonia

NSIP: Non specific interstitial pneumonia

Organizing Pnuemonia

Bronchiectasis, nodules

?PPFE pleuroparenchymal fibroelastosis:

Pleural inflammation/effusions: RA, SLE

Pericardial effusion or esophageal dilatation

CT severity correlates with survival in many diseases

Walsh S L F…Wells, Hansell. *Thorax* 2014, Cogliati et al. *Rheumatology* 2014
Moazedi-Fuerst F *Clin Exp Rheum* 2015, Doyle & Dellaripa *Chest* 2017

Radiology

Disease Associations:

UIP: RA or SSc, ANCA vasculitis

NSIP: RA, Systemic Sclerosis (SSc), Autoimmune myositis, Sjogren's, mixed connective tissue disease

OP: RA, Autoimmune myositis

Bronchiectasis, nodules: RA, Sjogren's

?PPFE pleuroparenchymal fibroelastosis: SSc, Sjogren's

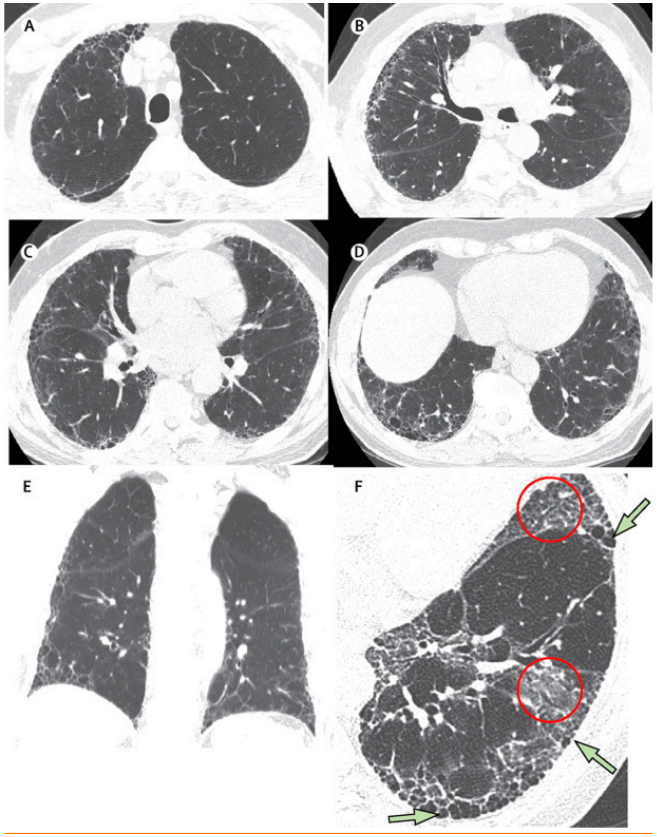
Pleural inflammation/effusions: RA, SLE; sometimes SSc

Pericardial effusion or esophageal dilatation: SSc, MCTD

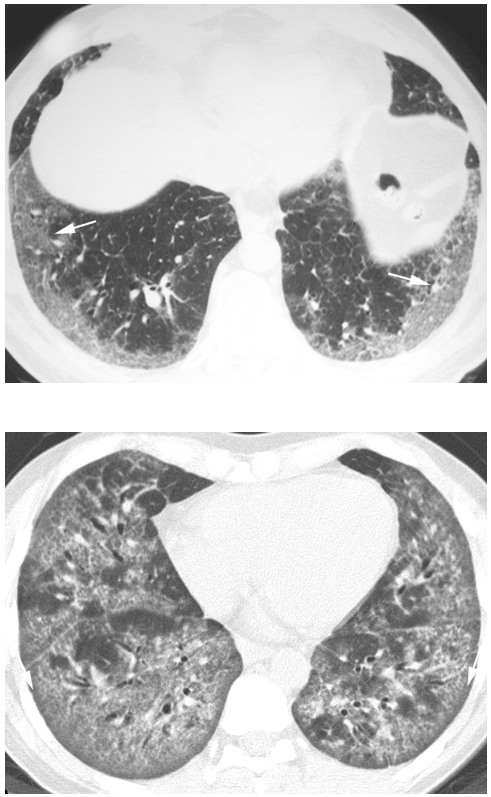
Walsh S L F…Wells, Hansell. *Thorax* 2014, Cogliati et al. *Rheumatology* 2014
Moazedi-Fuerst F *Clin Exp Rheum* 2015, Doyle & Dellaripa *Chest* 2017

Radiology in ILD: UIP vs NSIP

Typical UIP



Classic NSIP



Gotway et al. Thorax 2007;62:546-553 Lynch…Wells *Lancet Respir Med* 2018 Feb;6(2):138-153.

Typical Labs for CTD-ILD

- Workup for specific CTDs
  - RF, CCP for rheumatoid arthritis
  - ANA, SCL-70, others for scleroderma, lupus, Sjogren's
- "Myositis panel" - takes 3 weeks
  - anti-synthetase antibodies, MDA5
- General care
  - Liver function tests, kidney function, white blood cell count, red cell count
- Pre-treatment:
  - Hep B, TB screen

Detailed labs by disease

General	CMP, CBC with diff, CRP/ ESR
Vasculitis	ANCA, urinalysis
Rheumatoid arthritis	Rheumatoid factor (over 2x normal) Anti-Cyclic Citrullinated Peptide
Systemic Sclerosis	ANA (high titer) nucleolar pattern, anti centromere, Scl-70 /topoisomerase I, U3-RNP/fibrillarin, Th/To, RNA polymerase III
Sjögren's	ANA, dsDNA, Ro52/Ro60/SSA La/SSb, Ku
Mixed Connective Tissue Disease	ANA, **U1RNP**, Ro60
Systemic Lupus Erythematosus	ANA, dsDNA, Smith, Ro60, U1RNP, Ku
Idiopathic inflammatory myositis	CPK, aldolase, anti-cytoplasmic stain on ANA Ro-52/SSa, Ku, PM-Scl, U1RNP, U2RNP SRP, Mi-2, TIF1γ/α (p155/140), MDA5
Anti synthetase syndrome	Jo-1, PL-12, PL-7, OJ, EJ, KS, ZO, YRS (HA)

Red = data suggests seen more in patients with ILD

Treatments for CTD-ILDs

Steroids: Most common first agent especially for RA, myositis

Typically start at 0.5-1 mg/kg, taper slowly

Azathioprine: Steroid sparing agent, used for myositis, RA

Typically start at 50 mg, increase to 150 mg – goal 2mg/kg/day

Mycophenolate mofetil (MMF): steroid sparing agent.

Review for all CTD-ILD: stabilized/ improved FVC; decreases steroid dose; becoming first line in SSc

Typically start at 500 mg bid, increase to 1000 mg max 1500 mg bid

Fischer et al. *J Rheumatol.* 2013, Daoussis et al.*Clin Exp Rheumatol. 2012* Vij & Strek *Chest* 2013, Gutsche et al. *Cur Resp Care Rep* 2012, Hamblin & Horton *Pulm Med* 2011, Kim et al *Chest* 2009

Treatments for CTD-ILDs

IVIG: Recommended for refractory myositis

Case reports in ILD

Tacrolimus: Case series U Chicago 17 pts (12 myositis)

Recent Japanese case series 26 pts with in mild CTD-ILD improvement in most

Rituximab: Series of 33 CTD-ILD : 85% refractory to therapy

18% overall improved - 50% of myositis patients

Series of 24 patients; 15 with RA; no clear effect

Case reports in Sjogren's, LIP; small series in SSc

often 1 gram day 1 and day 14

Lung Transplant: similar survival to IPF in RA-ILD, SSc-ILD

Chartrand et al *Sarcoidosis Vasc Diffuse Lung Dis*. 2016, Keir et al *Respirology* 2014, Hallowell RW, *Ann Am Thorac Soc*. 2016 Oct;13(10):1682-1688. Labirua-Iturburu *Clin Exp Rheumatol*. 2013, Witt et. Al *Pulm Pharmacol Ther.* 2016 Yamano et al. *Respirology* 2018 Yazadani *J Heart Lung Transplant*. 2014, Khan *Respir Med*. 2013 Jablonski et al Current Opinion in Rheumatology 2018,

Specific Connective Tissue Diseases

Lots of ILD:

- Systemic Sclerosis (SSc)
- Rheumatoid Arthritis (RA)
- Idiopathic inflammatory myopathies
  - Antisynthetase Syndrome, MDA5

Some ILD:

- Sjögren's Syndrome
- Mixed Connective Tissue Disease (MCTD)
- Systemic Lupus Erythematosus (SLE)

Rheumatoid Arthritis (RA)

Clinical signs: joint deformity, nodules, morning stiffness

Labs: Rheumatoid factor (RF) over 3x normal; anti-cyclic-citrullinated peptide antibodies (anti- CCP) more common in ILD

Other Pulmonary involvement: Bronchiectasis/bronchiolitis, nodules

Rate of ILD in RA : 10-20% overall up to 60% in patients with symptoms

ILD can precede systemic symptoms (10%).

CT scan pattern: UIP pattern dominates; linked to worse outcome

Pathology: UIP, NSIP, OP, bronchiolitis

Prognosis: Median survival : 2.3–5 years after ILD diagnosis if UIP pattern on HRCT or biopsy. 10% of RA deaths are ILD

Risk of infections: prednisone >=10 mgs, OP pattern increased risk

Mathai and Danoff *BMJ* 2015, Mori et al. *Resp Med* 2012, Bongartz et al. *Arthritis & Rheumatism* 2010, Kouduri et al. *Rheum* 2010, Gochuico et al. *Arch Int Med 2008*, Cottin et al. *ERS* 2010, Kim et al. *ERS* 2010, Olson et al. *AJRCCM* 2010; Nakamura et al *Res Med* 2012

Systemic Sclerosis (SSc)

Clinical types: **Diffuse scleroderma** defined by skin changes in upper arm

Limited: skin changes only in forearm

Used to be known as "CREST" for Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasias)

Scleroderma sine scleroderma - no skin changes, but other manifestations

All forms can have ILD

Other pulmonary manifestations: Pulmonary hypertension

Esophageal dysmotility -> GERD might drive aspiration and ILD

Diagnostic Labs: Anti-nuclear antibodies ("ANA"), often high titer, nucleolar pattern, centromere pattern

anti- Scl-70 (topoisomerase) more likely ILD, anti centromere less likely

anti-Th/To, RNA polymerase II

anti-U2-RNP, PM-ScL, anti-Ku in overlap with myositis

Wells et al. *Sem Resp Critical Care* 2014, Strek et al. *Chest* 2013, Steen et al. *Ann Rheum Dis* 2007, Fischer et al. *Chest* 2006

Systemic Sclerosis (SSc)

Rate of ILD: In European registry ILD seen in 53% of diffuse SSc 35% of limited SSc; similar in Korean registry

90% ILD by autopsy. 85% of Scl-70/topoisomerase I positive

CT findings Basilar predominant ground glass and reticulations (90%); some honeycombing

Pathology: mostly fibrotic NSIP; also UIP, DAD, COP

Prognosis: Divided by "minimal" or "extensive" lung disease

HRCT : Involved lung < or > 20% of total

if CT indeterminate, use FVC < or > 70%

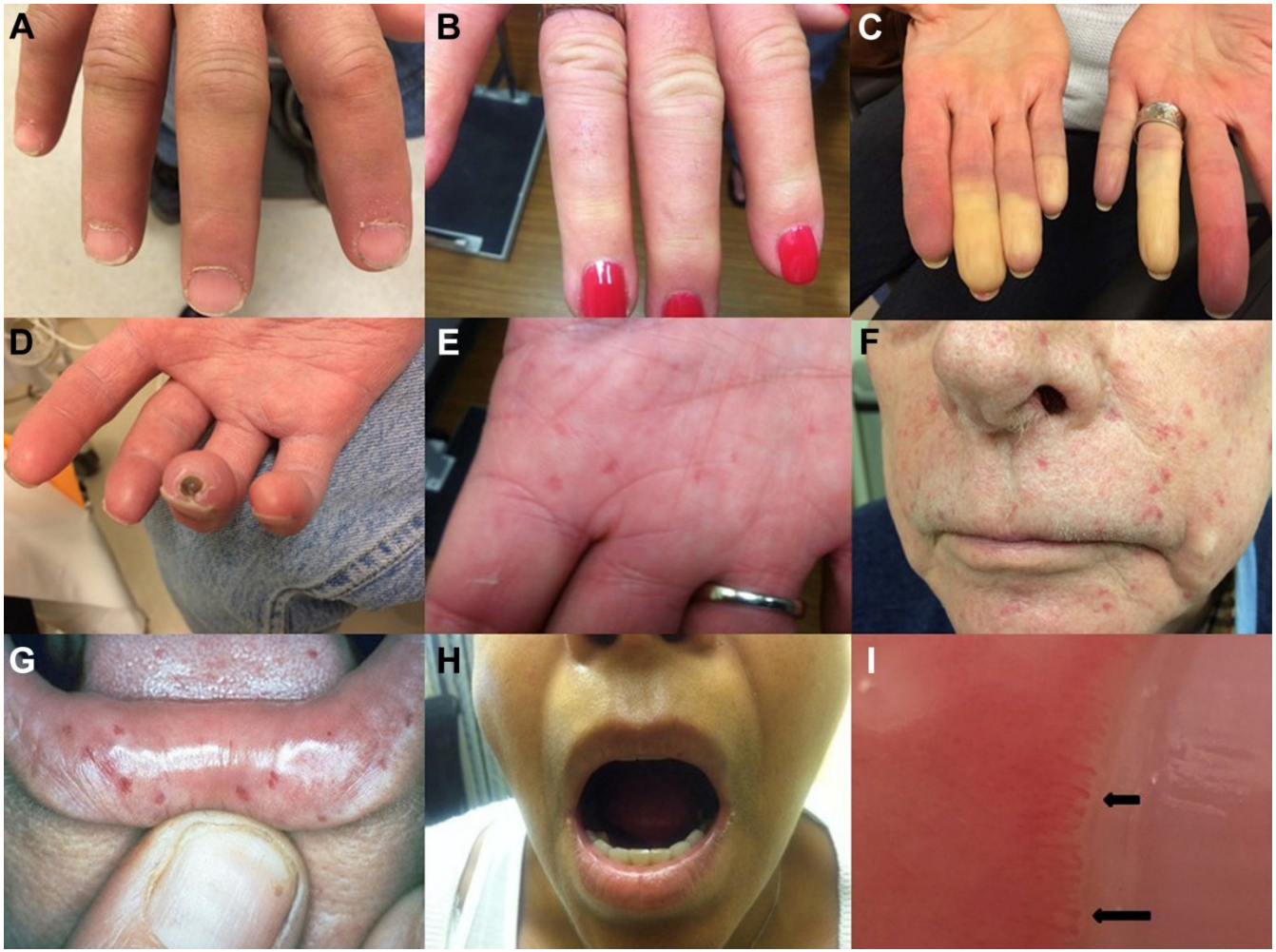
No clear correlation of pathology/CT pattern and death

Progression highest in first 4 years of disease

DLCO better prognostic marker than FVC

Hant et al. *Clin Chest Med* 2010, Walker et al. *Ann Rheum Dis* 2007
Winstone et al *Chest* 2014, Bouros et al. *AJRCCM* 2002
Goh et al. *AJRCCM* 2008

Systemic sclerosis Clinical Images



Tracy J. Doyle and Paul F. Dellaripa *Chest* 2017

Systemic sclerosis: image key

A, Sclerodactyly; note the lack of vertical skin creases on the extensor surfaces of the fingers
B, Active Raynaud syndrome with sclerodactyly.
C, Sharp demarcation in perfusion of the distal digits in a patient with active Raynaud syndrome.
D, Ischemic ulceration in a patient with severe Raynaud syndrome.
E, Palmar telangiectasia.
F, Facial telangiectasia.
G, Telangiectasia on the lip and tongue.
H, Limited oral aperture (limited ability to open mouth)
I, Dilated nail fold capillaries, suggests vasculopathy seen in scleroderma and other rheumatic syndromes

Tracy J. Doyle and Paul F. Dellaripa *Chest* 2017

Idiopathic Inflammatory Myopathies

Clinical signs

Proximal muscle weakness: diagnose by EMG, biopsy, MRI
Dermatomyositis: can see skin changes Gottron's papules, heliotrope rash
Clinically amyopathic dermatomyositis: skin findings, likely ILD

Labs: Elevated CPK, aldolase
Myositis Specific / Associated Antibodies: Mi-2, SRP, Ro-52
MDA-5/CADM-140, 155/140
PM/Scl, Ku : overlap with systemic sclerosis (Myositis panels available)

In one study, of 165 pts with idiopathic ILD at ILD center: 26% had a + myositis antibody

Other pulmonary manifestations: cough, acute pneumonitis, pneumomediastinum (DM)

Rate of ILD: 20–75%, **may precede myositis in up to 18%**

CT findings: Ground glass, micronodules, reticulations

Prognosis: Majority resolve or improve (~20% deteriorate)

Acute ILD has mortality up to 73%. 5 year mortality up to 50%

Fidler et al. *Lung* 2019, Satoh et al *Clin Rev Allergy Immunol*. 2017 Hallowell *Sem Resp Critical Care* 2014, Marie et al. *Arthritis Care & Res* 2002, 2005, *Sem Arth Rheum* 2012, Danoff & Casciola-Rosen *Arthritis Res Ther*. 2011,

Antisynthetase Syndrome

Clinical: Seen in 40% of dermatomyositis/polymyositis
Inflammatory myositis, elevated CPK,
GI involvement, polyarthritis, fevers, mechanic's hands

Diagnostic Labs: Anti-aminoacyl-tRNA synthetase antibodies
Anti-Jo-1, PL-7, PL-12, KS, OJ commonly associated with ILD

Rate of ILD: 67-86%; **often precedes systemic symptoms**
Muscle symptoms may not match respiratory symptoms

HRCT: NSIP pattern, basilar predominance; peripheral ground glass

Pathology: NSIP, UIP, COP, DAD, LIP

Prognosis: 30% remission with therapy, relapse possible
Jo-1 better, +PL-7 or +PL-12, older, UIP pattern on HRCT worse

Ongoing trial seeking environmental triggers – Brigham, Hopkins. NCT01276470

Hallowell et al. *Sem Resp Critical Care* 2014, Hall et al. *Arthritis Care Res,* Marie et al. *Autoimmunity Rev* 2012, Marie et al. *Eur J Int Med* 2013, Fischer et al. *Resp Med* 2009, Connors et al. *Chest* 2010, Danoff & Casciola-Rosen *Arthritis Res Ther*. 2011

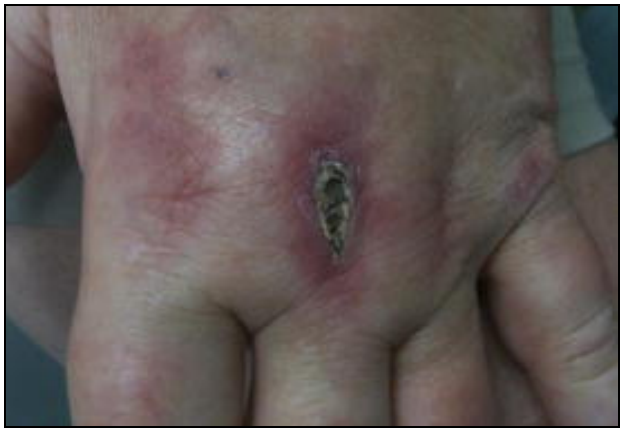
MDA5+ Dermatomyositis

Clinical: 13% of dermatomyositis patients in Pittsburgh cohort.

With or without muscle symptom

Symmetric involvement of many joints

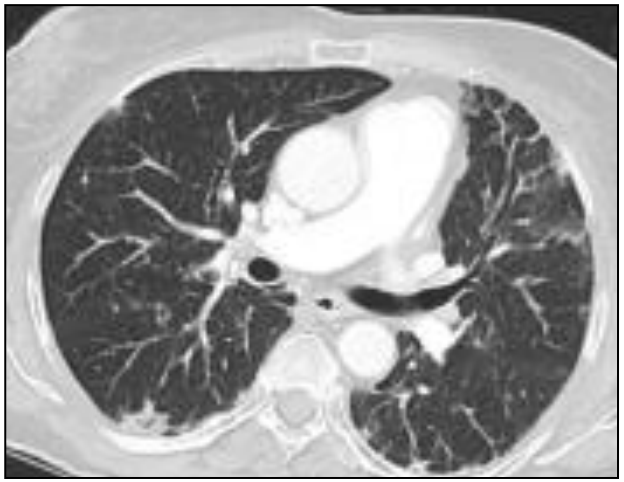
Skin ulcers



Labs: MDA5 (CADM-140), may have anti-cytoplasmic pattern on ANA stain

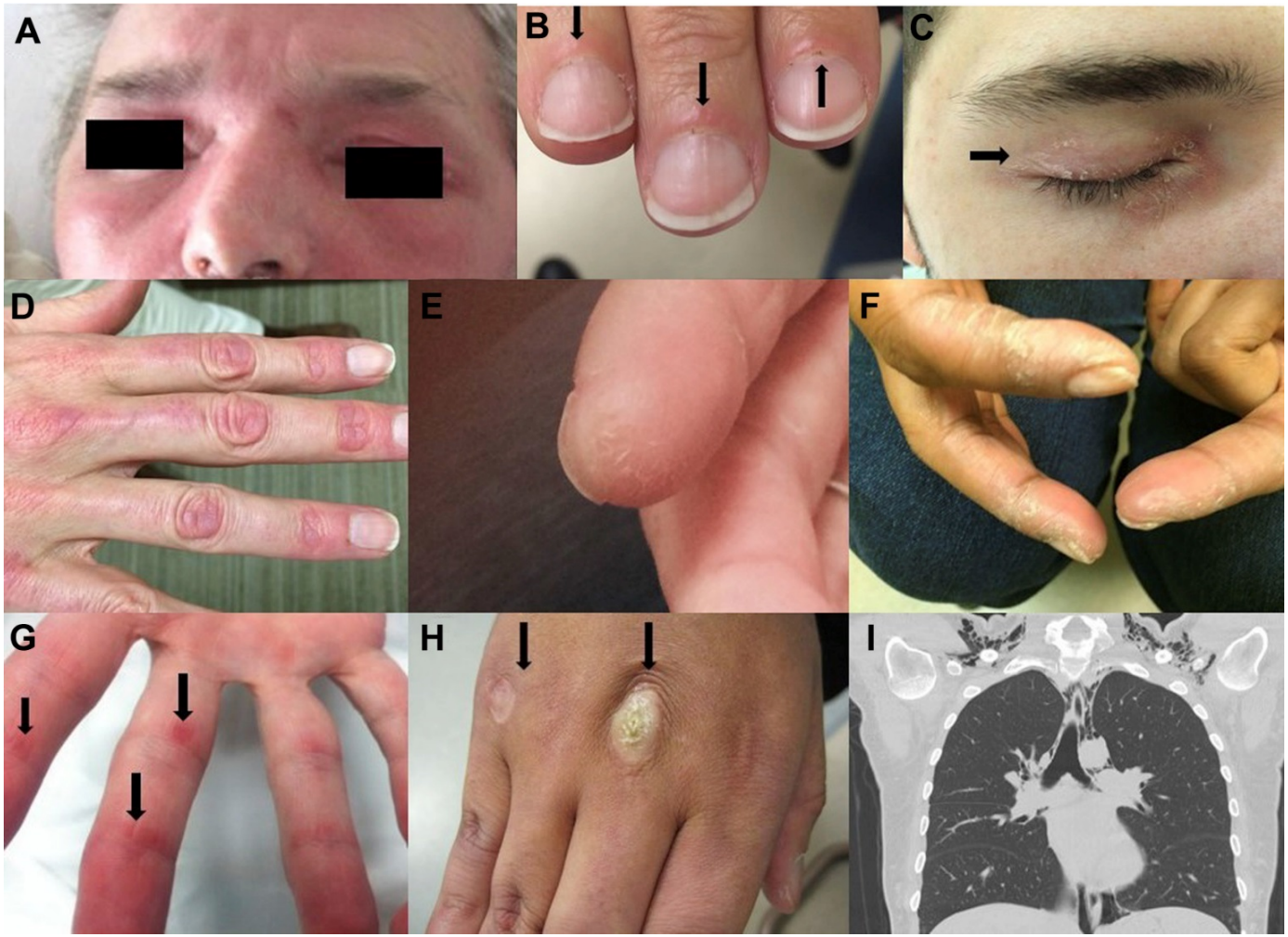
ILD: Significant association with MDA5 (50% in one cohort)

Prognosis: Rapid progression very common



Moghadam-Kia S et al. *J Rheumatol.* 2017 , *Arthritis Care Res* 2016; Narang et al *Arthritis Care Res* 2015 May, Hall et al. *Arthritis Care Res* 2013, Chaisson et al *Medicine* 2012

Autoimmune myositis: clinical findings



Tracy J. Doyle and Paul F. Dellaripa *Chest* 2017

Autoimmune myositis: image key

A, Diffuse erythema (redness): of the face in a patient with dermatomyositis and interstitial lung disease (ILD).
B, Periungual erythema (redness around the fingernail) (down arrows) of fingers and ischemic vascular changes (up arrow) in the periungual area in a patient with dermatomyositis.
C, Eyelid erythema and scaling seen in dermatomyositis.
D, Gottron papules over the extensor surfaces of the fingers with periungual erythema in dermatomyositis.
E, Cracking in the distal tips of the fingers of a patient with antisynthetase syndrome: “mechanics hands.”
F, Mechanics hands in the antisynthetase syndrome.
G, Nodular erythematous lesions on the palmar surface of the hand seen in melanoma differentiation-associated gene 5 (MDA5) antibody-related ILD.
H, Healing ulcerating plaques on the dorsal surface of the hand in a patient with MDA-5 antibody-related ILD.
I, Pneumomediastinum in dermatomyositis.

Image key modified slightly from excellent review from Tracy J. Doyle and Paul F. Dellaripa *Chest* 2017

Sjogren's Syndrome (SS)

Clinical signs Keratoconjunctivitis sicca syndrome (lymphocytic infiltration of glands). Overall more common in women.

Diagnostic Labs: ANA, anti-Ro/SSa, anti-La/SSb, RF

Other pulmonary: xerotrachea (dryness in throat), dry cough

Rate of ILD: estimates vary widely (8–75%); reduced FVC and DLCO in 17–37.5%. Males with Sjogrens disproportionately affected with ILD

HRCT: ground glass most common, LIP pattern of nodules/cysts, or frank bronchiectasis; lower lobe predominant

Pathology: NSIP, UIP (may have both) LIP, amyloid; lymphoma

Prognosis: often mild, limited disease without severe decline; UIP not necessarily worse than other patterns. May develop lymphoma

Kreider & Highlands *Sem Resp Crit Care* 2014, Enomoto et al *PLoS One*. 2013; Palm et al. *Rheumatology* 2013, Yazisiz et al. *Rheum Int* 2010, Parambil et al. *Chest* 2006, Cain et al. *Clin Chest Med* 1998

Systemic Lupus Erythematosus (SLE)

Clinical: Serositis (inflammation of lining of lung or heart) anemia, malar rash (rash on cheeks), kidney disease

Diagnostic Labs: ANA, anti-Smith, anti-dsDNA

Other pulmonary manifestations: pleurisy (inflammation of lining of lung (50%), acute pneumonitis, bleeding in lung, "shrinking lung"

Rate of ILD: 30% have restrictive disease on PFTs, 18%] ILD on CT scan. More common in late-onset (age >50) disease

HRCT: NSIP pattern, effusions,

Pathology: usually NSIP, UIP, LIP, can see DAH

Prognosis: Overall appears less progressive than other CTD-ILD, except in overlap syndromes

Medlin, *Semin Arthritis Rheum*. 2018 , Mittoo S, Fell CD. *Semin Respir Crit Care Med*. 2014, Antin-Ozerkis et al. *Clin Chest Med* 2012, Allen et al. *Lupus* 2012, Gutsche et al. *Cur Resp Care Rep* 2012

Mixed Connective Tissue Disease (MCTD)

Clinical signs: can be any mix of SLE, myositis, Systemic Sclerosis

Raynaud's, polyarthritis, myositis, esophageal dysmotility

Labs: ANA, anti-U1 RNP

Other pulmonary: pulmonary hypertension, pleural effusions

Rate of ILD: Up to 41% by CT scan, fibrosis; increased in men, higher RNP, +Ro52, 20% may have severe fibrosis.

HRCT: NSIP pattern: reticulations, ground glass; subpleural micronodules; peripheral lower lobes.

Path: no large series

Prognosis: increased mortality if severe fibrosis on HRCT (20% in 4 year follow up)

Kozuka et al. *J Thor Imaging* 2001, Szodary et al. *Lupus* 2012, Fagundes et al. *Res Med* 2009, Gunnarsson et al. *Ann Rheum Dis* 2012, Sem Rheum 2018H ant et al. *Clin Chest Med* 2010

Interstitial Pneumonia with Autoimmune Features

Term for Autoimmune-seeming ILD, not fitting rheumatology criteria

"**Clinical, Serologic, and Morphologic**" features

Clinical: Raynaud's, puffy finger, morning stiffness, mechanic hands, digital ulcerations Gottron's etc.

Serologic: ANA >1:320, ANA nucleolar or centromere pattern, RF >= 2x, CCP, dsDNA, SSA/SSB, PM-Scl, RNP, Sm, ScL-70, antisynthetase, MDA5

Morphologic:

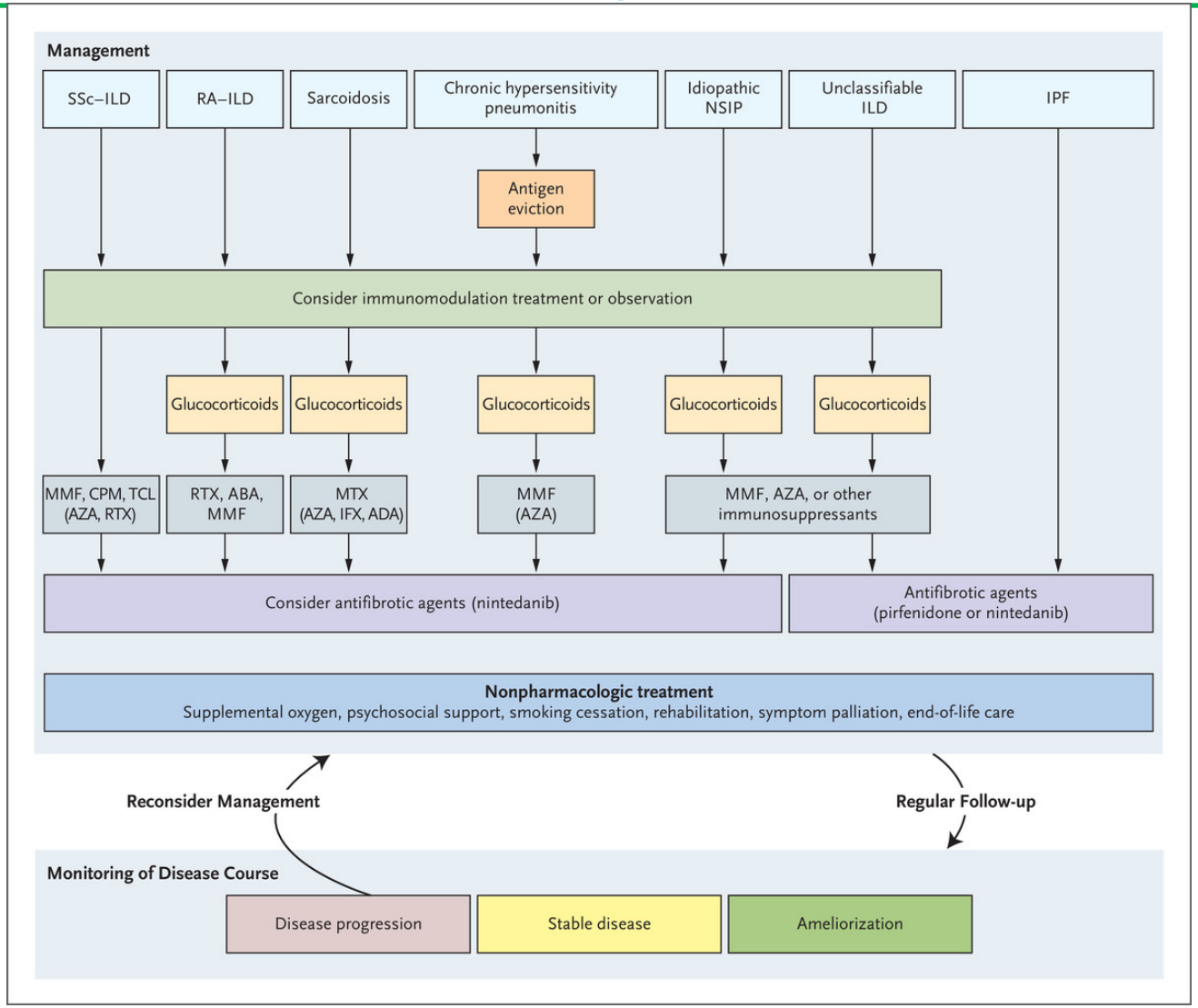
Radiology: NSIP, OP, NSIP/OP, LIP UIP not exclusionary.

Pathology: NSIP, OP, NSIP/OP, LIP, lymphoid aggregates, lymphoplasmacytic infiltration

Multicompartment involvement (airways, pleura, pericardium vasculature)

Graney and Fiscjer *Ann Am Thorac Soc.* 2019
Adegunsoye et al. *AM J Path* 2017, Fisher et al. *Eur Respir J*. 2015
Fischer et al. *Chest* 2012, Vij et al. *Chest* 2011, Fischer & du Bois *Lancet* 2012
Kinder et al. *AJRCCM* 2007, Corte et al. *ERJ* 2012

Overview of Management of ALL Pulmonary Fibrosis



M Wijsenbeek, V Cottin. N Engl J Med 2020;383:958-968.

Take home points

- Autoimmune - specifically connective tissue diseases- commonly lead to ILD
- Ideally pulmonary and rheumatology experts work closely together to diagnose and treat
- Knowing there is an underlying CTD may change treatment
  - Might add anti-inflammatory/immune suppressing medications
  - Might still use anti-fibrotic medication as in IPF