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

Ways to look for CTD

History

Physical Exam

Radiology

Pathology

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

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

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

Moazed-Fuerst F *Clin Exp Rheum* 2015, Doyle & Dellaripa *Chest* 2017
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

Moazedi-Fuerst F *Clin Exp Rheum* 2015, Doyle & Dellaripa *Chest* 2017
Radiology in ILD: UIP vs NSIP

Typical UIP

Classic NSIP

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

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

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

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 **Calcinosi**s, 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

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

Goh et al. AJRCCM 2008
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
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%

**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

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

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

Systemic Lupus Erythematous (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

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)

**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)

Grane and Fiscer *Ann Am Thorac Soc.* 2019  
Overview of Management of ALL Pulmonary Fibrosis

Management

SSc–ILD
RA–ILD
Sarcoidosis
Chronic hypersensitivity pneumonitis
Idiopathic NSIP
Unclassifiable ILD
IPF

Antigen eviction

Consider immunomodulation treatment or observation

Glucocorticoids
Glucocorticoids
Glucocorticoids
Glucocorticoids
Glucocorticoids

MMF, CPM, TCL (AZA, RTX)
RTX, ABA, MMF
MTX (AZA, IFX, ADA)
MMF (AZA)
MMF, AZA, or other immunosuppressants

Consider antifibrotic agents (nintedanib)
Antifibrotic agents (pirfenidone or nintedanib)

Nonpharmacologic treatment
Supplemental oxygen, psychosocial support, smoking cessation, rehabilitation, symptom palliation, end-of-life care

Reconsider Management

Regular Follow-up

Monitoring of Disease Course

Disease progression
Stable disease
Ameliorization
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