RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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Rheumatoid Arthritis Associated Interstitial Lung Disease

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OBJECTIVES

1. The importance of pulmonary evaluation in patients with CTD
2. What types of imaging to consider
3. Review of common RA associated pulmonary diseases
4. Types of RA-ILD? Clarify imaging patterns
5. Therapeutics for RA-ILD
6. Is Methotrexate our friend or foe?
7. Why not new lungs? Consideration for lung transplant

CASE

48-year-old male, presented to pulmonary clinic in 2014, with dyspnea and hypoxemia. Recent ICU admit, on vent, for PNA

ROS: DOE. no joint pain. No Raynaud's

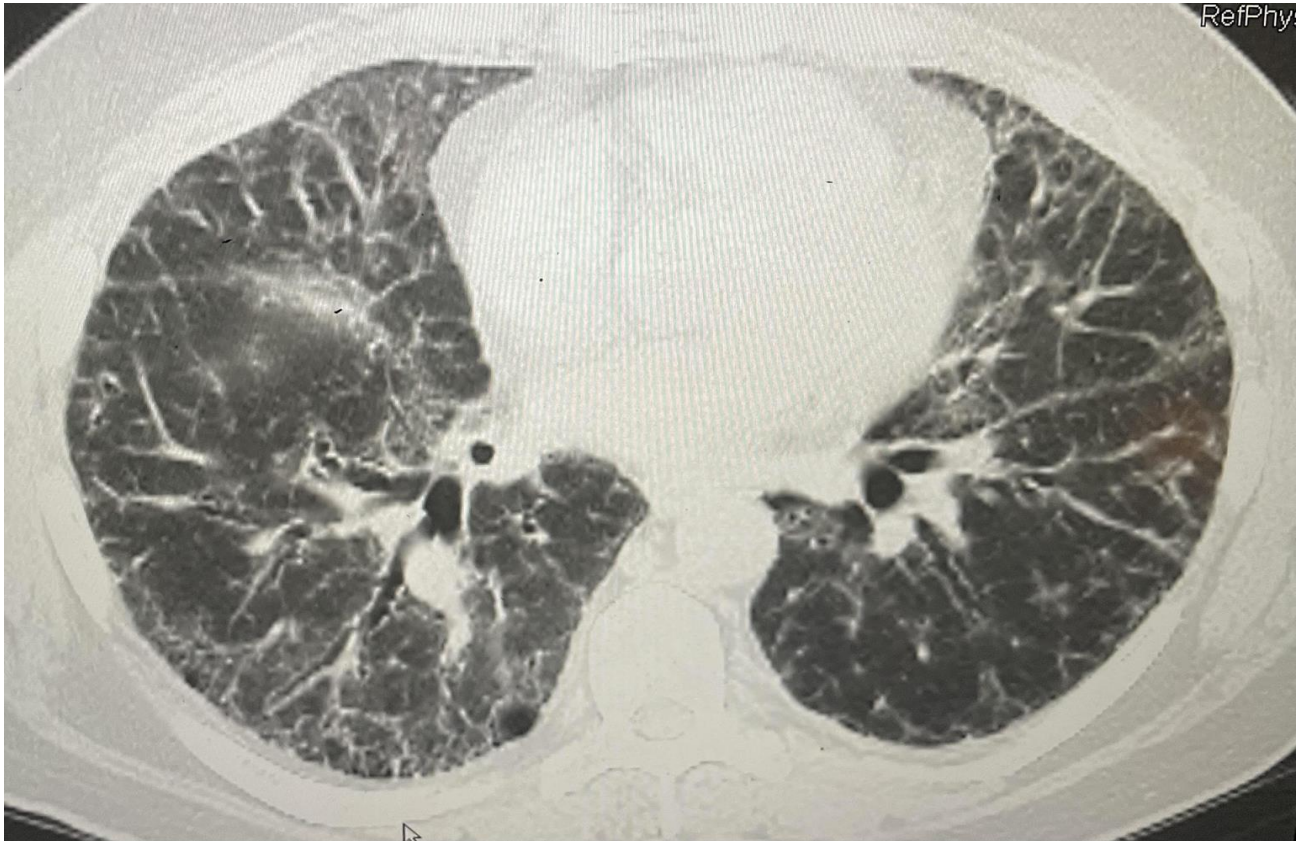
PMH: alcoholism (sober now), recurrent pneumonia. HCV+. Obesity

Social history: former smoker, 20 pack/year. quit in the last year. Hx meth use. Worked as a scrapper

Family history: Aunt and sister with RA

Labs: ANA 1:80, nucleolar, CCP 22, RF neg. Myositis, SCL70, SSA/SSB all neg.
* ~ 5 years later, negative ANA. RF 105, CCP 56

- **PFT**: FVC 3.05L, 70%; FEV1 2.73L, 80%; FEV1/FVC 90. **DLCO 54%**
- **Imaging**: HRCT-Fibrosing interstitial pneumonia c/w UIP pattern. 2 nodules
- **Gas exchange**: RA sat at rest 91%, nadir 84% w/exertion. Required 4L with activity
- **Exam**: bibasilar crackles, clubbing
- **Does he have RA-ILD ? What are the next steps ?**


RefPhy

Pulmonary Evaluation in Patients With CTD, Why Is This Important?

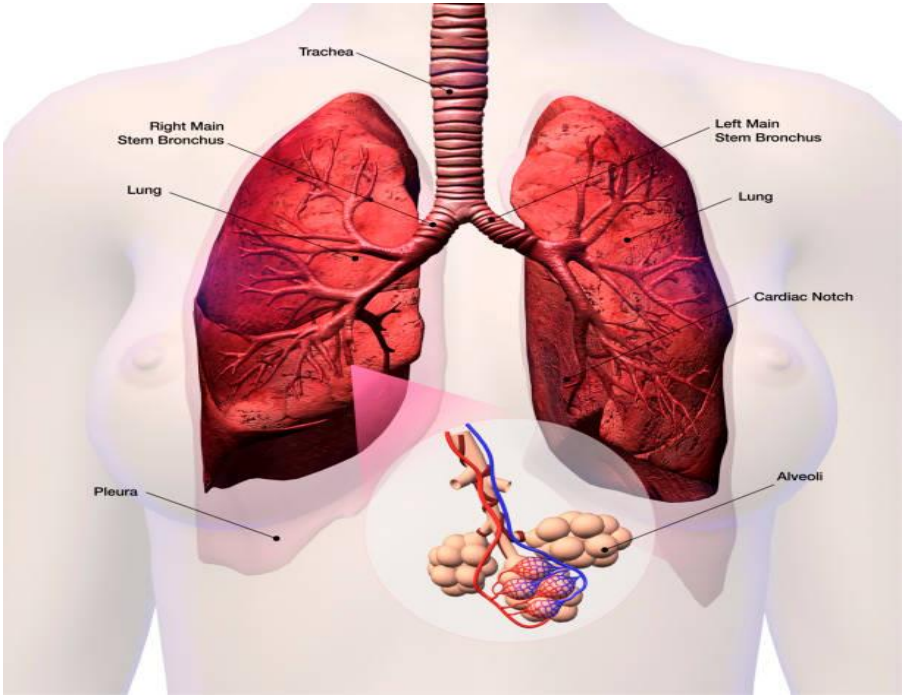
CTD can affect all compartments in the lung

Airways: bronchiolitis, bronchiectasis

Pleura: pleuritis, pleural effusions

Vasculature: pulmonary HTN, pulmonary embolism

Interstitium: UIP, NSIP, LIP, OP, DAH



Interstitial Lung Disease Evaluation

IMAGING: CXR to start. CT imaging required: **HRCT** preferred. Concern for PE ?, get CTA

PFT'S: Airways:obstruction. ILD: Restriction

BRONCHOSCOPY:
In RA, mostly to r/o infection. Useful if dx unclear
Envisia can show UIP pattern when the CT is indeterminate

LABS: CBC, CMP, ESR, CRP, RF, CCP, ANA,ENA (SSA,SSB,RNP, Sm), SCL70* (Scl 12 panel), Myositis Panel. If concern for vasculitis, ANCA w/MPO and PR3

ASSESS OXYGEN STATUS
Rest, Exertion, overnight

CARDIAC EVAL/ECHO
CV disease leading cause of death in RA
PH shown to have worse prognosis w/IPF. Can point towards CTD/scleroderma

SURGICAL LUNG BIOPSY?
avoid in high risk pt (↑02 need, PH, ↓FVC, ↓DLCO)

MULTIDISCIPLINARY CONFERENCE

ILD-Pulm, Rheum, Radiology, Pathology

Common Pulmonary Manifestations in CTD

	ILD	Airways	Pleural	Vascular	DAH
Systemic sclerosis	+++	–	–	+++	–
Rheumatoid arthritis	++	++	++	+	–
Primary Sjögren's syndrome	++	++	+	+	–
Mixed CTD	++	+	+	++	–
Polymyositis/ dermatomyositis	+++	–	–	+	–
Systemic lupus erythematosus	+	+	+++	+	++

The signs show prevalence of each manifestation (– = no prevalence; + = low prevalence; ++ = medium prevalence; +++ = high prevalence). ILD = interstitial lung disease; DAH = diffuse alveolar haemorrhage; CTD = connective tissue disease.

Table 1: CTDs and common pulmonary manifestations.

Fischer A and Du Bois R. *Lancet.* 2012.

Table 1. Features of the most common connective tissue disease associated interstitial lung diseases			
	SSc-ILD	**RA-ILD**	**PM/DM-ILD**
Common HRCT and Pathologic Pattern	NSIP	UIP	NSIP with OP
Pathologic findings	Bland pauci-cellular fibrosis uniformly throughout interstitium, with preservation of alveolar architecture	Usual interstitial pneumonia pattern with lymphoid aggregates and germinal centers	Typical nonspecific interstitial pneumonia pattern
Risk factors	Anti-topoisomerase	Smoking High titer CCP Male sex	Anti-Jo1 Anti-PL-12
Prevalence	Up to 90%	19-58%	Up to 75%
Outcome	5-year survival 85%	5-year survival 36% in UIP and 94% in NSIP	5-year survival 60 to 80%

Solomon et al. *ATS CTD-ILD Primer.* 2021.

Rheumatoid Lung Involvement

Airways

Cricoarytenoiditis

Constrictive or follicular bronchiolitis

Bronchiectasis

Vasculature
Pulmonary vasculitis
Pulmonary HTN

Pleura
Pleuritis, effusions

Interstitium
UIP, NSIP, OP, LIP
Nodules

Malignancy
RA patients have increased risk for lung cancer

Pulmonary Embolism
High risk DVT and PE
Risk is highest in the first year after diagnosis, then declines

Infections
Immunosuppressive therapy, CTD

COVID-19

Drug Induced Lung Injury
Symptoms can be acute, or years into treatment
Check pneumotox
May need bronch

Kadura and Raghu. *Eur Respir. Rev* 2021; Simon et al. *Arthritis Res Ther.* 2015;
Li et al. *Rheumatology.* 2021;Lake Up To Date 2021.

RA-ILD

ILD Patterns

UIP: usual interstitial pneumonia. ***Fibrotic***. (most common)

NSIP: Nonspecific interstitial pneumonia. ***Inflammatory***

OP: Organizing pneumonia

LIP: Lymphocytic interstitial pneumonia (rare, secondary Sjogren's)

Huang et al. *Curr Treatm Opt Rheumatol*. 2020.

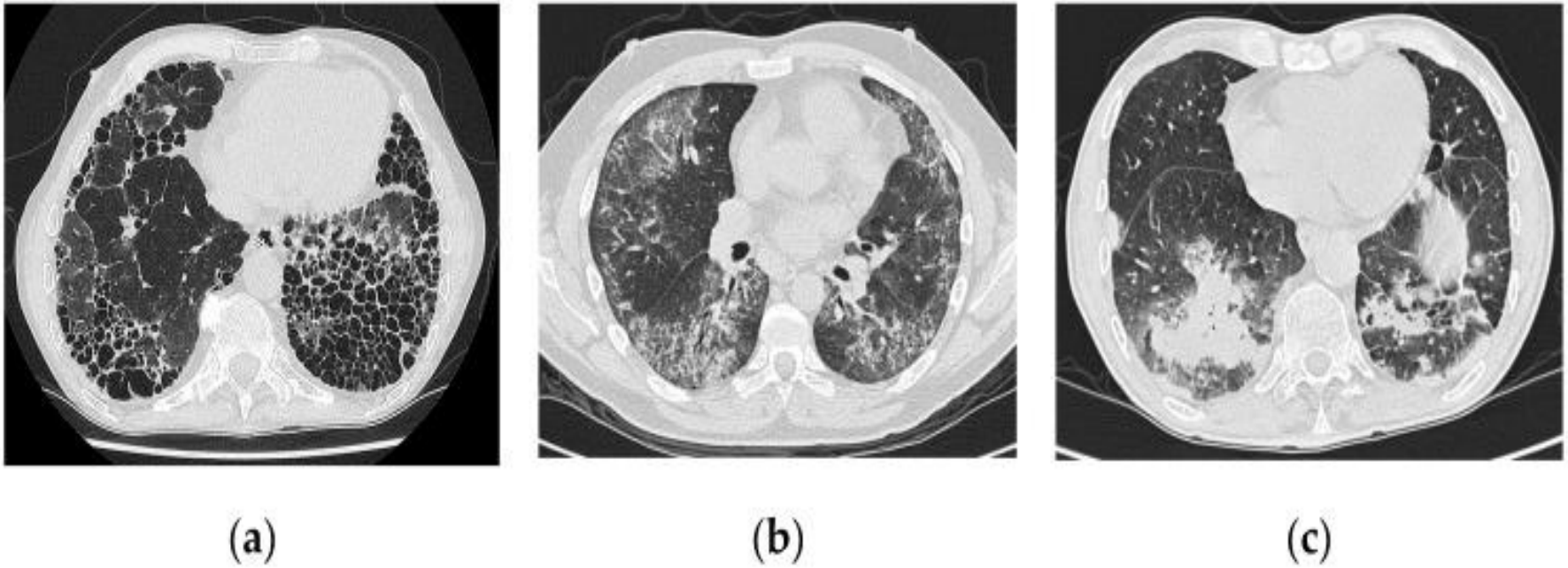
RA-ILD

- While RA affects more women than men, men tend to get RA-ILD
- Risk factors:
  - Older age
  - Male
  - Smokers *
  - High disease activity
  - Seropositive disease (CCP)
  - Family history/Genetic risk.
    *Biomarkers being studied

- **UIP pattern**
  - Portends a worse outcome than NSIP
  - Mean survival **3-7 years**
  - Associated with poor QOL, decreased functional capacity
- **NSIP pattern**
  - Improved response to treatment
  - Less risk for progression

Hyldgaard et al. *Ann Rheum Dis.* 2017; England and Herberger. *Curr Opin Rheumatol.* 2020;
Huang et al, *Curr Treatm Opt Rheumatol*. 2020; Salaffi et al. *Medicine*. 2019; Kadura & Raghu. *Eur Respir. Rev* 2021.

CT Example of RA-ILD



Bendstrup et al. *J.Clin.Med.* 2019.

Treatment of RA-ILD

Steroids

- May be beneficial in NSIP or OP.
- Should not be used for fibrotic ILD. PANTHER trial: ↑ risk of death in IPF, with prednisone, azathioprine, NAC
- Consider if acute exacerbation
- Please consider PJP prophylaxis

Rituximab

- Yusuf et al (2017): > 700 patients w/RA. 56 w/ILD
- Ritux showed stable/improved in ILD
- ILD that progressed, majority had PF-ILD before Ritux started

Mycophenolate mofetil

- Fischer et al: MMF in non-UIP pattern a/w improvement in FVC & DLCO. UIP pattern, stable
- Does not help joints

Additional Therapy

- Controversy on TNFi causing ILD vs improvement
- Thus far, no RCT's comparing therapies for RA-ILD

Huang et al. *Curr Treatm Opt Rheumatol.* 2020; Raghu et al. *N Engl J Med.* 2012; Yusuf et al. *Rheumatology.* 2017;
Fischer et al. *J Rheumatol*. 2013; England and Hersberger. *Curr Opin Rheumatol.* 2020; Kadura and Raghu. *Eur Respir. Rev* 2021.

Treatment for RA-ILD
Antifibrotics

Nintedanib

- INBUILD trial (2019) - rate of decline in FVC significantly lower in patient with PF-ILD
- Does not improve lung function, slows progression of decline
- Common s/e: diarrhea

Pirfenidone

- Maher et al: For non-classifiable ILD, showed slower decline in FVC
  Request for approval pending
- TRAIL trial: RCT looking at pirfenidone in RA-ILD. Stopped due to recruitment, impact of COVID. Final study data pending

Maher et al. *Lancet.* 2019; Flaherty et al. *N Engl J Med.* 2019; Kadura and Raghu. *Euro Repsir Rev.* 2021.

Methotrexate
Friend or Foe?

Methotrexate previously thought to cause ILD.

Rare, but possible for acute pneumonitis reaction; usually in days to weeks after starting, risk ↓ after first year.

Symptoms: fever, cough, dyspnea.

Resolves with stopping drug

Kieley et al (2019)- 2701 patients with RA. MTX not associated with ILD, and possibly delayed onset of ILD

Juge et al (2021)- Meta analysis, looked at >1000 patient with RA. MTX was not associated with risk for RA-ILD, and in patient on MTX, ILD was detected later

Fragoulis (2019)- Literature review. MTX not associated with ILD

Fragoulis, G. *Rheumatology.* 2019.
Kiely P et al. *BMJ Open.* 2019.
Juge et al. *Eur Respir J.* 2021.

Additional Therapeutic Interventions

- Smoking cessation
- Oxygen Therapy
- Pulmonary rehab
- Treat comorbid conditions
  - GERD, OSA
- Palliative care for advanced lung disease

COVID

- Increased risk for severe COVID in patients treated with Ritux
- Vaccines are recommended for patients with RA
  - Case reports of possible RA flare with mRNA vaccines
  - Li et al: large study with >5000 patients with RA. No association with vaccination and RA flare
- Consider Evusheld

Avouc et at. *Lancet Rheumatol.* 2021; Li X et al. *Ann Rheum Dis.* 2022.

Transplant – Why Not a New Set of Lungs?

Lung transplant consideration

- There is a high risk of death in next 2 years if transplant not done
- High likelihood for 90 day survival post transplant
- High likelihood of 5 year survival post transplant
- Yazdani et al: Similar survival post transplant with RA-ILD and IPF, and significant improvement in quality of life

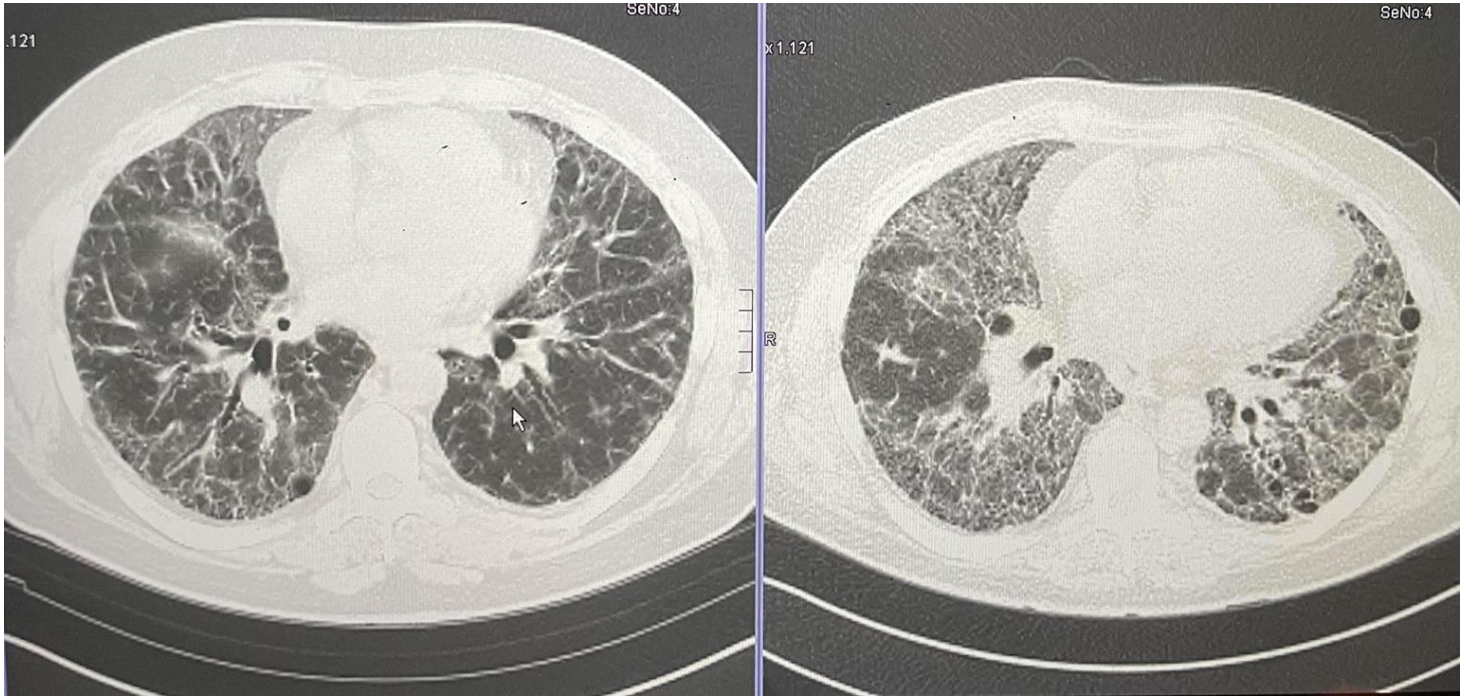
Transplant contraindication

- History of cancer, usually require 5 years cancer free
- CAD (not treated), other end organ disease (renal failure, cirrhosis)
- Drug/alcohol/tobacco use
- Active infections
- Obesity
- Lack of support, mental health issues
  Hep C not contraindicated if HCV treated

Yazdani et al. *J Heart Lung Transplant.* 2014; Weil. *Thorac Dis.* 2018.

Back to the Case

7 Years Later



Back to the Case

- Started on MMF initially
- 18 months after initial Rheum consult, he had diffuse synovitis with significant erosions. Hydroxychloroquine started
- Continued progression of ILD, Rituximab and Ofev added in early 2020.
- By 2020-2021, significant hypoxemia, required 15L + with exertion. **FVC 45 %, DLCO 32%**
- November 2021, successful bilateral lung transplant !

Summary

- The lungs can be affected by RA in multiple compartments
- All patients with RA lung involvement deserve a comprehensive evaluation by a pulmonologist
- RA-ILD greatly impacts both quality of life and life expectancy
- UIP patterns portends worse outcome. Early intervention with antifibrotic therapy may help
- Methotrexate is not thought to contribute to ILD, further research needed to determine if it can help protect against ILD
- Lung transplant may be an option for eligible patients
- Encourage COVID 19 vaccination series

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