Interstitial Pneumonia with Autoimmune Features (IPAF)

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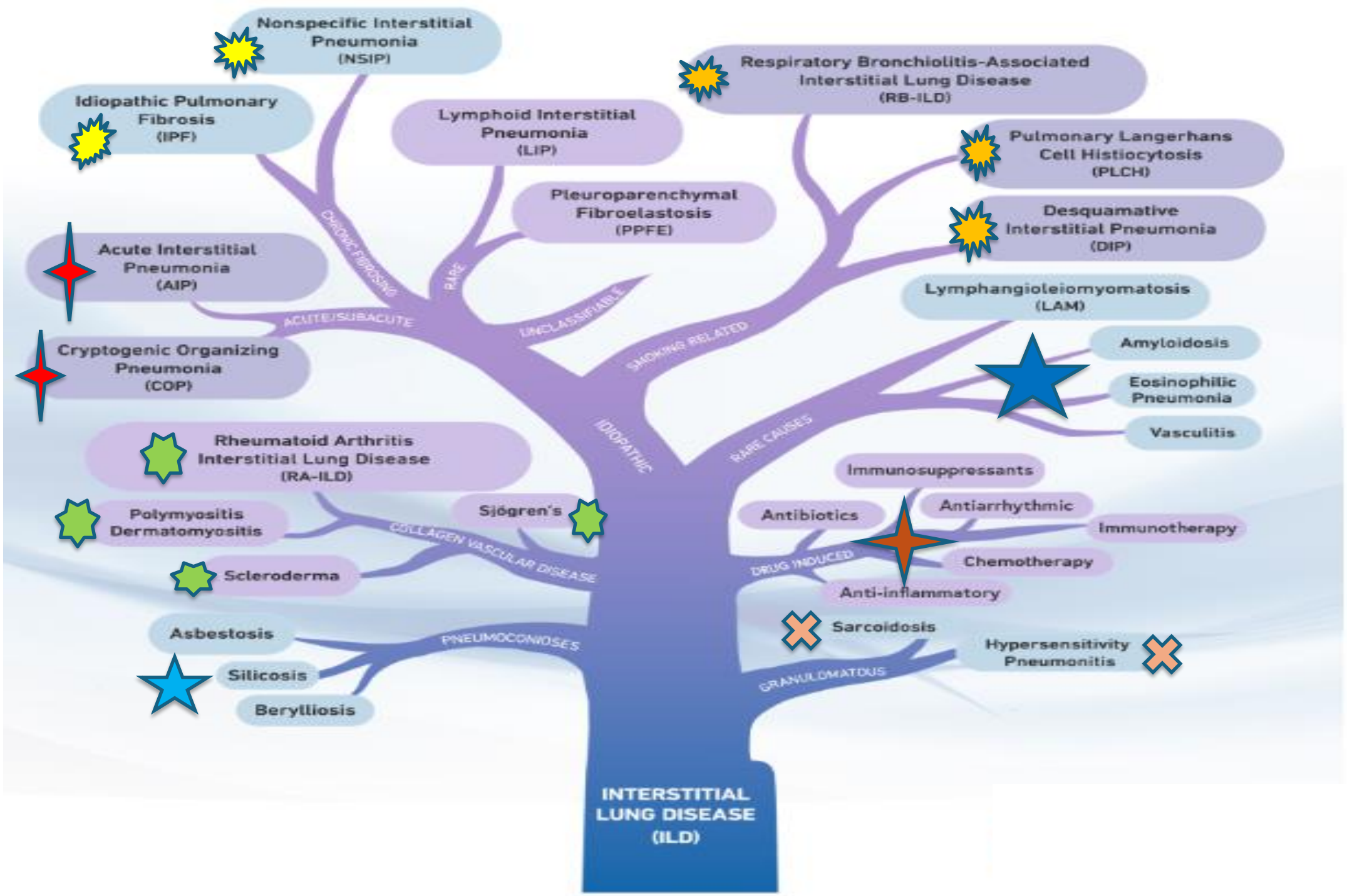
Objectives

1. Review various etiologies of ILD
2. Examine IPAF classification criteria
3. Review radiographic patterns in IPAF
4. Identify management strategies in IPAF
5. Discuss prognosis of IPAF
6. Explore areas of uncertainty and controversies in IPAF


Nonspecific Interstitial Pneumonia (NSIP)
Idiopathic Pulmonary Fibrosis (IPF)
Lymphoid Interstitial Pneumonia (LIP)
Respiratory Bronchiolitis-Associated Interstitial Lung Disease (RB-ILD)
Pulmonary Langerhans Cell Histiocytosis (PLCH)
Pleuroparenchymal Fibroelastosis (PPFE)
Desquamative Interstitial Pneumonia (DIP)
Acute Interstitial Pneumonia (AIP)
Lymphangioleiomyomatosis (LAM)
Cryptogenic Organizing Pneumonia (COP)
Amyloidosis
Eosinophilic Pneumonia
Vasculitis
Rheumatoid Arthritis Interstitial Lung Disease (RA-ILD)
Immunosuppressants
Antibiotics
Antiarrhythmic
Immunotherapy
Chemotherapy
Anti-inflammatory
Polymyositis Dermatomyositis
Sjögren's
Scleroderma
Sarcoidosis
Hypersensitivity Pneumonitis
Asbestosis
Silicosis
Berylliosis
CHRONIC FIBROSING
RARE
UNCLASSIFIABLE
ACUTE/SUBACUTE
SMOKING RELATED
IDIOPATHIC
RARE CAUSES
COLLAGEN VASCULAR DISEASE
DRUG INDUCED
PNEUMOCONIOSES
GRANULOMATOUS
INTERSTITIAL LUNG DISEASE (ILD)

Background

Many ILD patients present with clinical, serological, and/or radiological features suggestive of CTD but lack features to meet the established diagnostic criteria of defined CTD

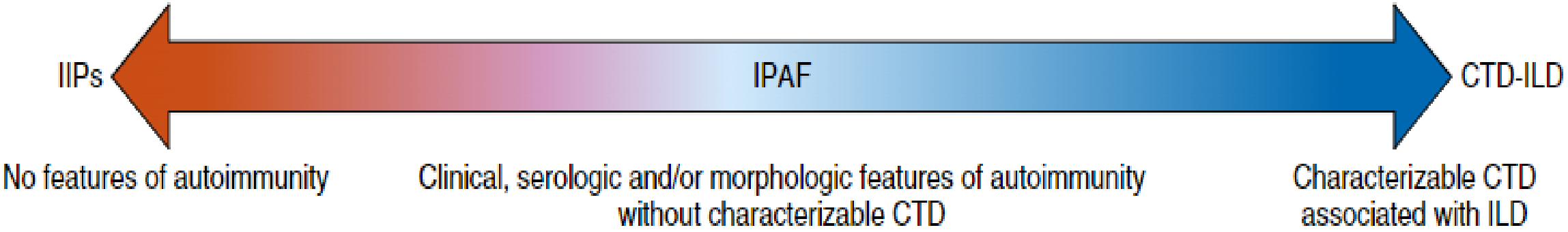
25% of pts with features of a systemic AI disease do not fulfill ACR classification criteria for CTD

10– 20% of pts with idiopathic interstitial pneumonia (IIP) have systemic symptoms and serologic abnormalities suggestive of an autoimmune process

Undifferentiated CTD-ILD

Early CTD-ILD

Lung- dominant CTD

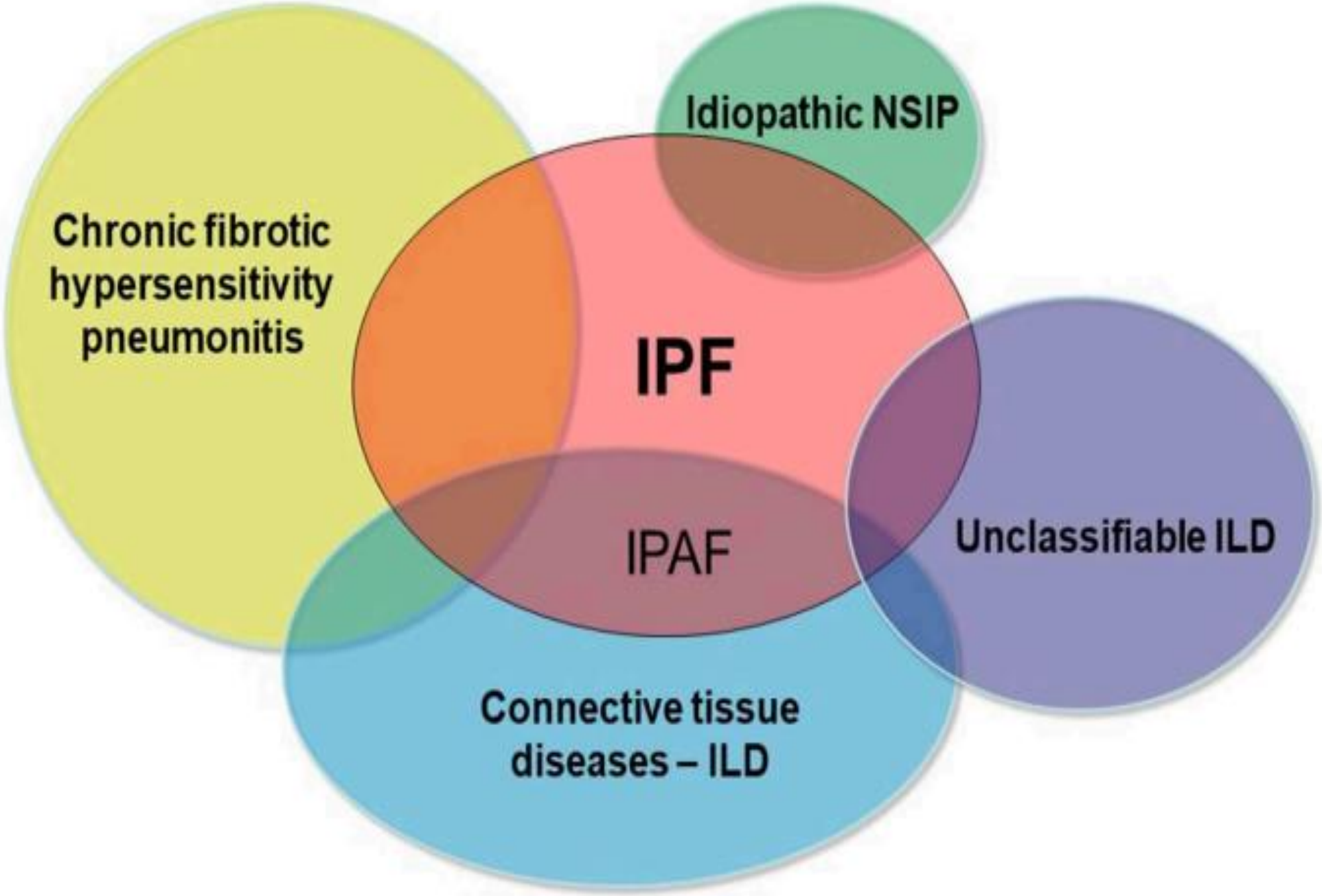


Autoimmune-featured ILD

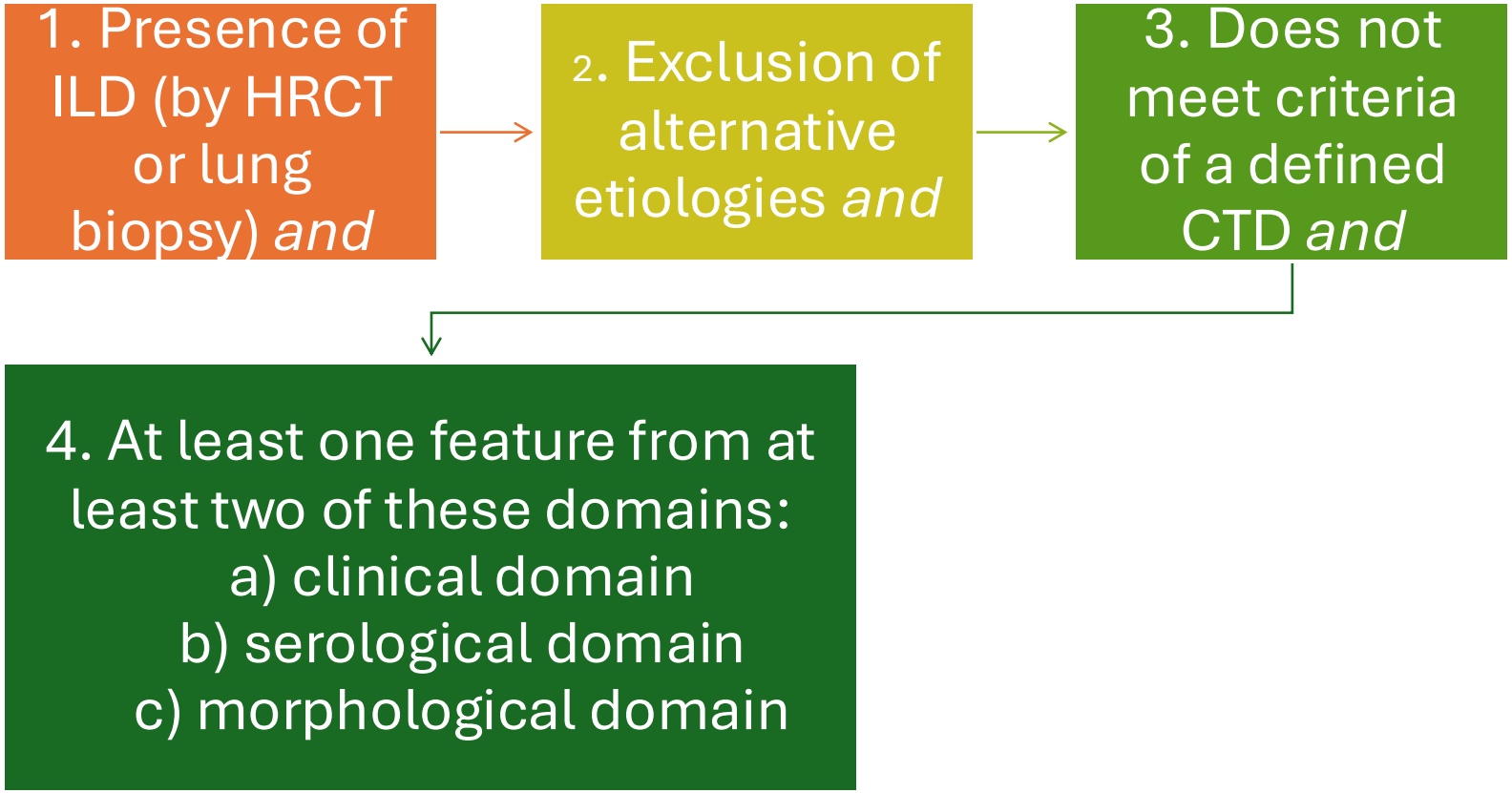
“Formes frustes” of CTD

IPAF

- In 2015, the ERS and ATS *“Task force on undifferentiated forms of CTD-associated interstitial lung disease”* proposed classification criteria for a “research category” of Interstitial Pneumonia with Autoimmune Features (IPAF)

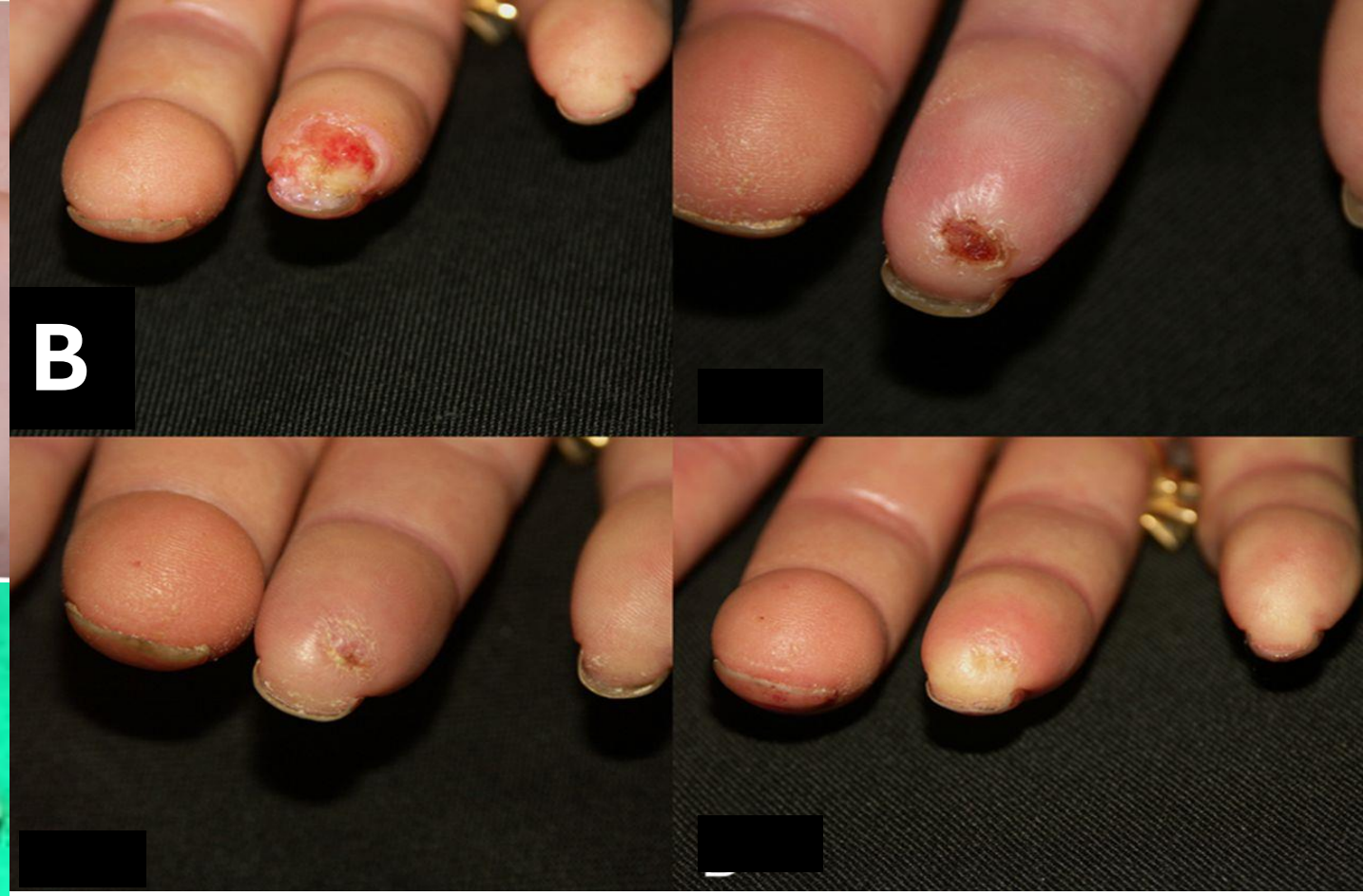

Idiopathic NSIP
Chronic fibrotic hypersensitivity pneumonitis
IPF
IPAF
Unclassifiable ILD
Connective tissue diseases – ILD

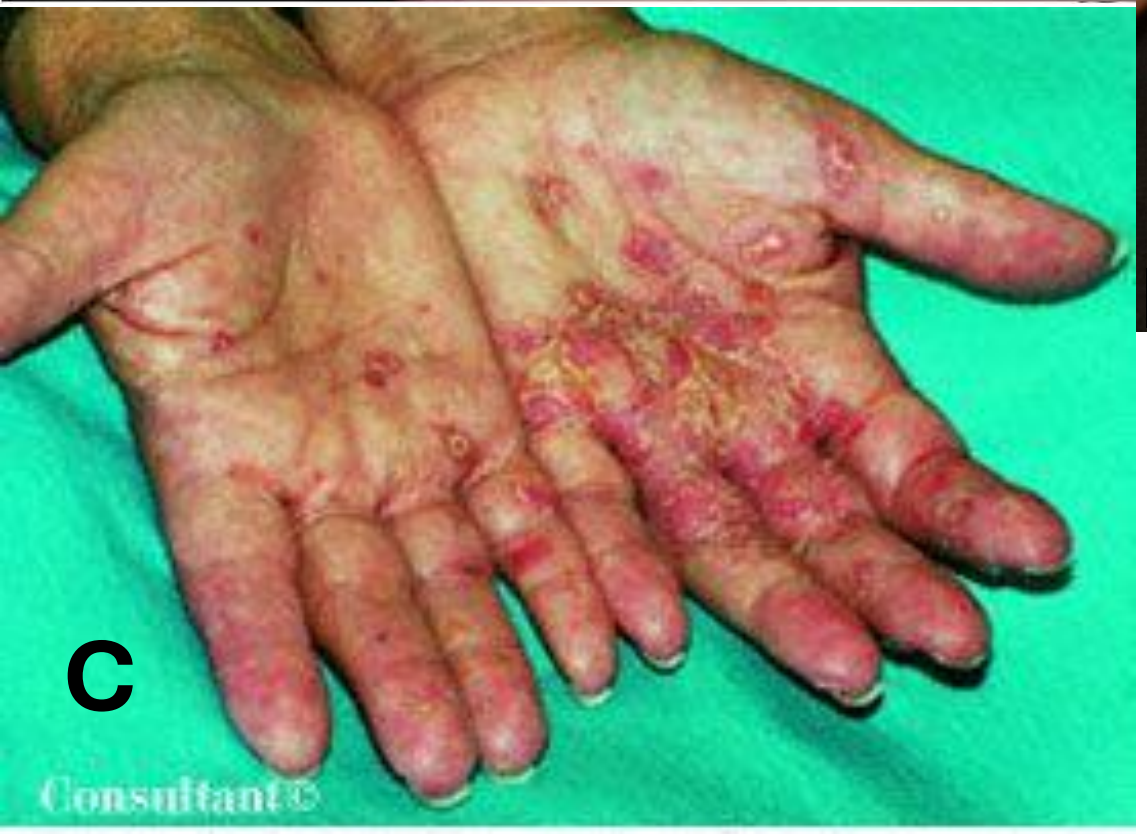
IPAF classification



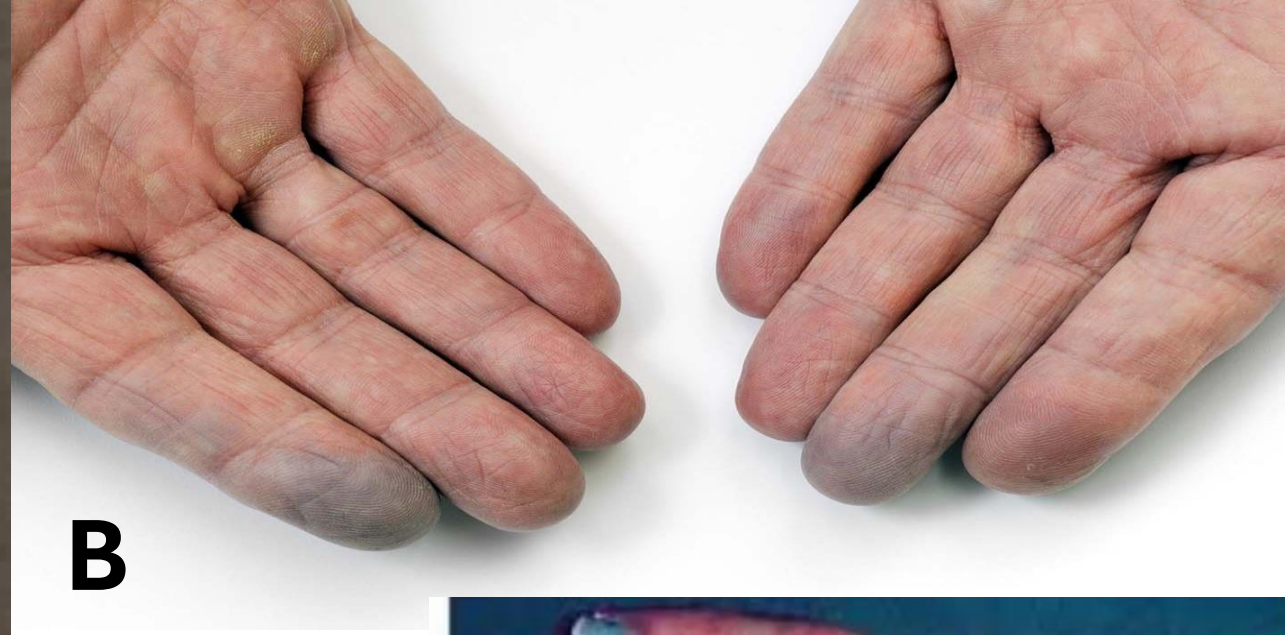
Clinical Domain

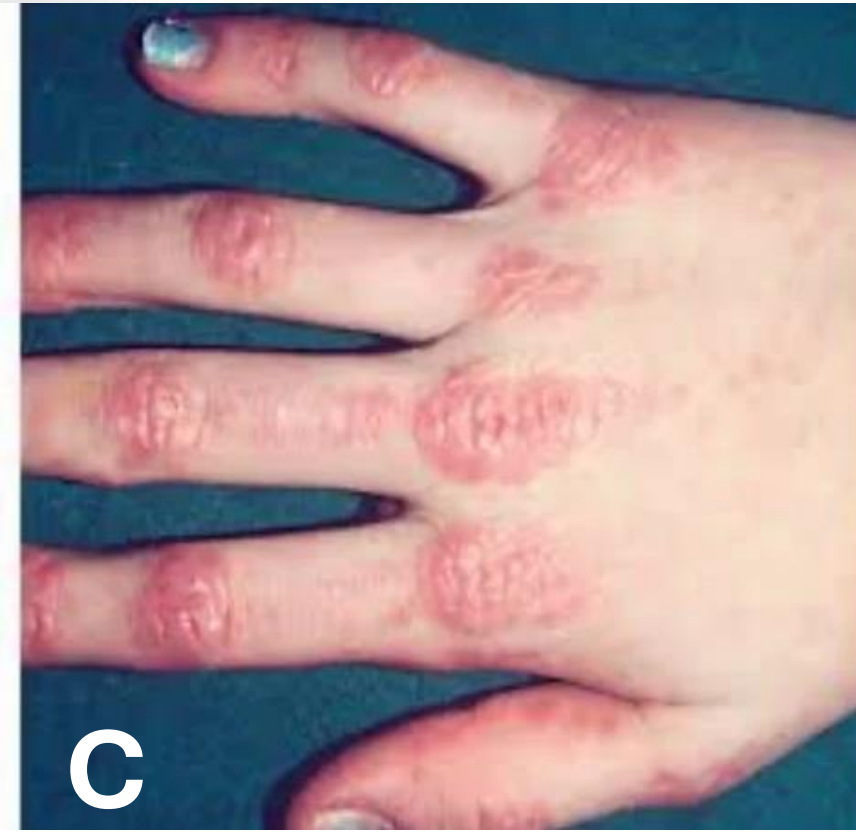
- Distal digital fissuring (*i.e.* “mechanic hands”)
- Distal digital tip ulceration
- Inflammatory arthritis *or* polyarticular morning joint stiffness ≥60 min
- Palmar telangiectasias
- Raynaud's phenomenon
- Unexplained digital edema
- Unexplained fixed rash on the digital extensor surfaces (Gottron's sign/papules)





A) Mechanic's hands
B) Digital ulceration
C) Palmar telangiectasias





A) and B) Raynaud's disease
C) Gottron's papules

Clinical Domain

Consists of extrathoracic features that suggest underlying CTD, but on their own are not diagnostic

Less-specific features that were included in prior classification schemes (e.g., joint pain, myalgias, weight loss, photosensitivity, and sicca symptoms) were not included

Task force suggested that presence of clinical features should be assessed on physical examination and that self reported sx should not be credited

Serologic Domain

- ANA ≥1:320 titer, diffuse, speckled, homogeneous patterns *or*
  1) ANA nucleolar pattern (any titer) *or*
  2) ANA centromere pattern (any titer)

- Rheumatoid factor ≥2× upper limit of normal
- Anti-CCP
- Anti-dsDNA
- Anti-Ro (SS-A)
- Anti-La (SS-B)
- Anti-ribonucleoprotein
- Anti-Smith
- Anti-topoisomerase (Scl-70)
- Anti-tRNA synthetase (*e.g.* Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
- Anti-PM-Scl
- Anti-MDA-5

Serologic Domain

90% of patients with IPAF have at least one of the serological criteria

MC antibodies: high titer ANA, high titer RF, Anti-SSa, antisynthetase antibodies

The domain excludes nonspecific markers of inflammation (ESR/CRP)

For less-specific antibodies—ANA and RF—sufficiently high titers are required to fulfill the criteria

ANA + with diffuse homogeneous or speckled pattern at low titer can be found in healthy control subjects, healthy elderly patients, and patients with IPF

Morphologic Domain

1) Suggestive HRCT radiology patterns:

- NSIP, OP, NSIP with OP overlap, LIP

2) Histopathology patterns by lung biopsy:

- NSIP, OP, NSIP/OP overlap, LIP, Interstitial lymphoid aggregates with germinal centers, Diffuse lymphoplasmacytic infiltration

3) Multi-compartment involvement:

a. Unexplained pleural effusion or thickening

b. Unexplained pericardial effusion or thickening

c. Unexplained intrinsic airways disease (by PFT, imaging or pathology)

d. Unexplained pulmonary vasculopathy

Morphologic Domain

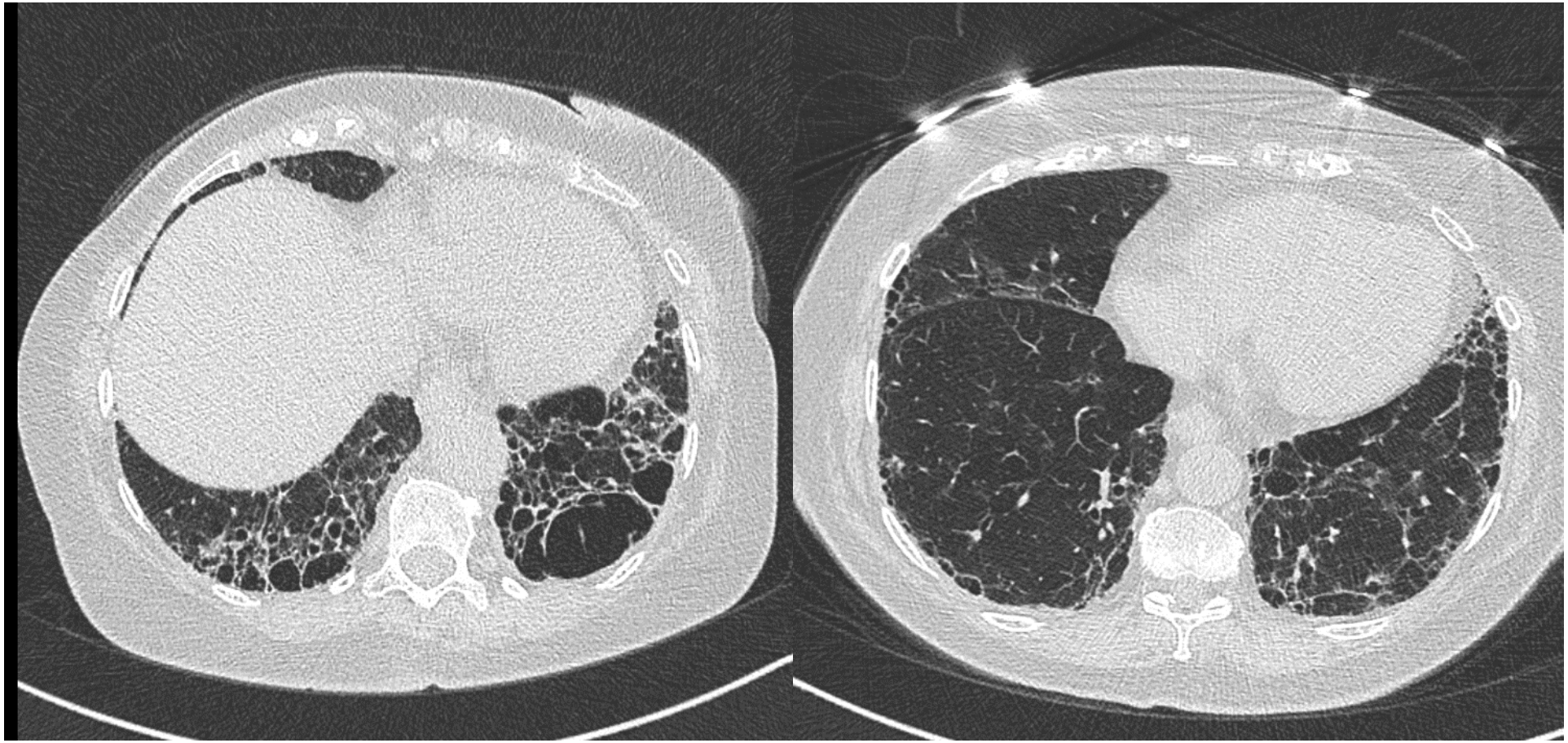
NSIP pattern at HRCT and/or histopathology was the most frequent finding in several series

Although UIP pattern on HRCT is MC pattern in RA-ILD, it was not given the same weight as other patterns because it is less specific for CTD

UIP does not exclude an IPAF designation but there is no morphological "credit" given to it

Histologic UIP pattern observed in IPAF patients is often non-typical, with diffuse lymphoplasmacytic infiltration, interstitial lymphoid aggregates, or histological involvement of the airways

Usual Interstitial Pneumonia (UIP)



Subpleural and basilar predom location, reticular pattern with traction bronchiectasis/bronchiolectasis, +/- honeycombing, can have mild GGO

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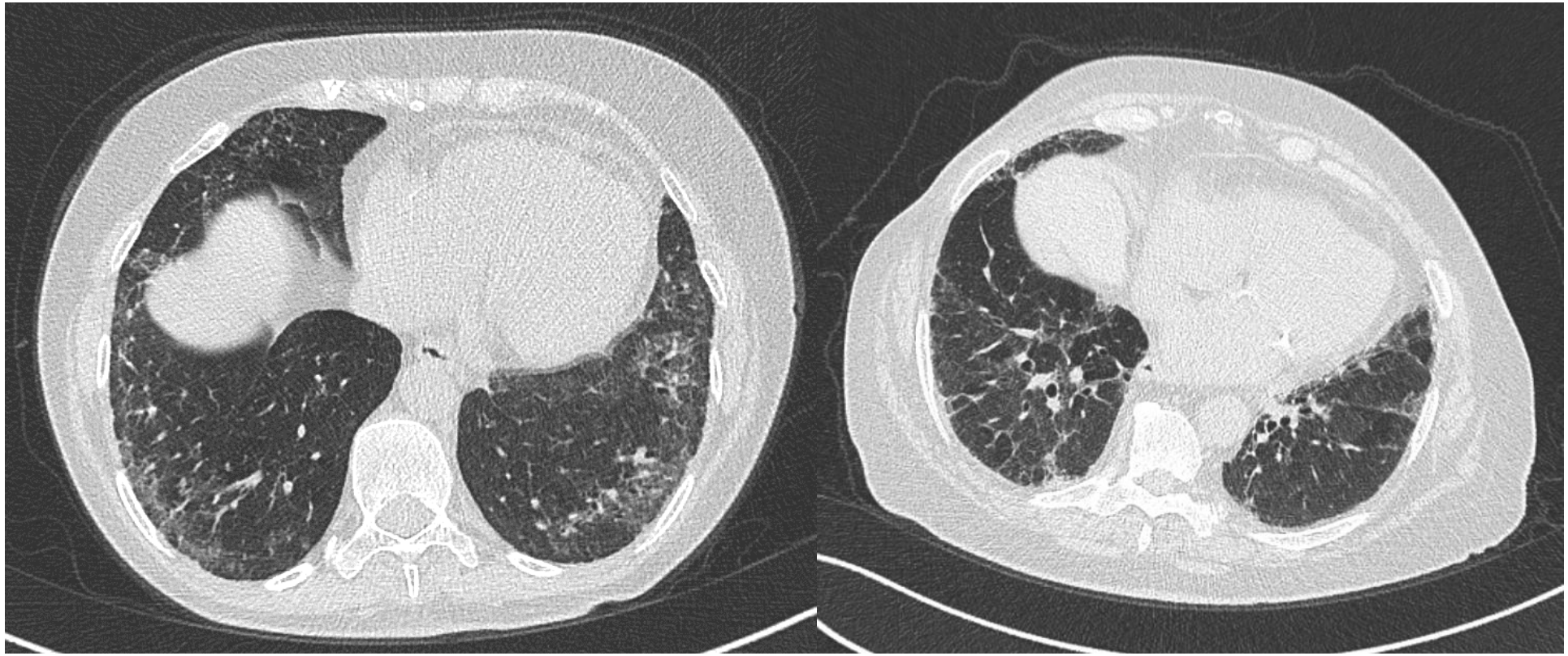
Non-specific Interstitial Pneumonia (NSIP)



Bilateral GGO, basilar and peripheral distribution, but can involve upper lobes, mostly symmetrical, occasionally with subpleural sparing, traction bronchiectasis, lung volume loss when fibrosis extends from hilum periphery

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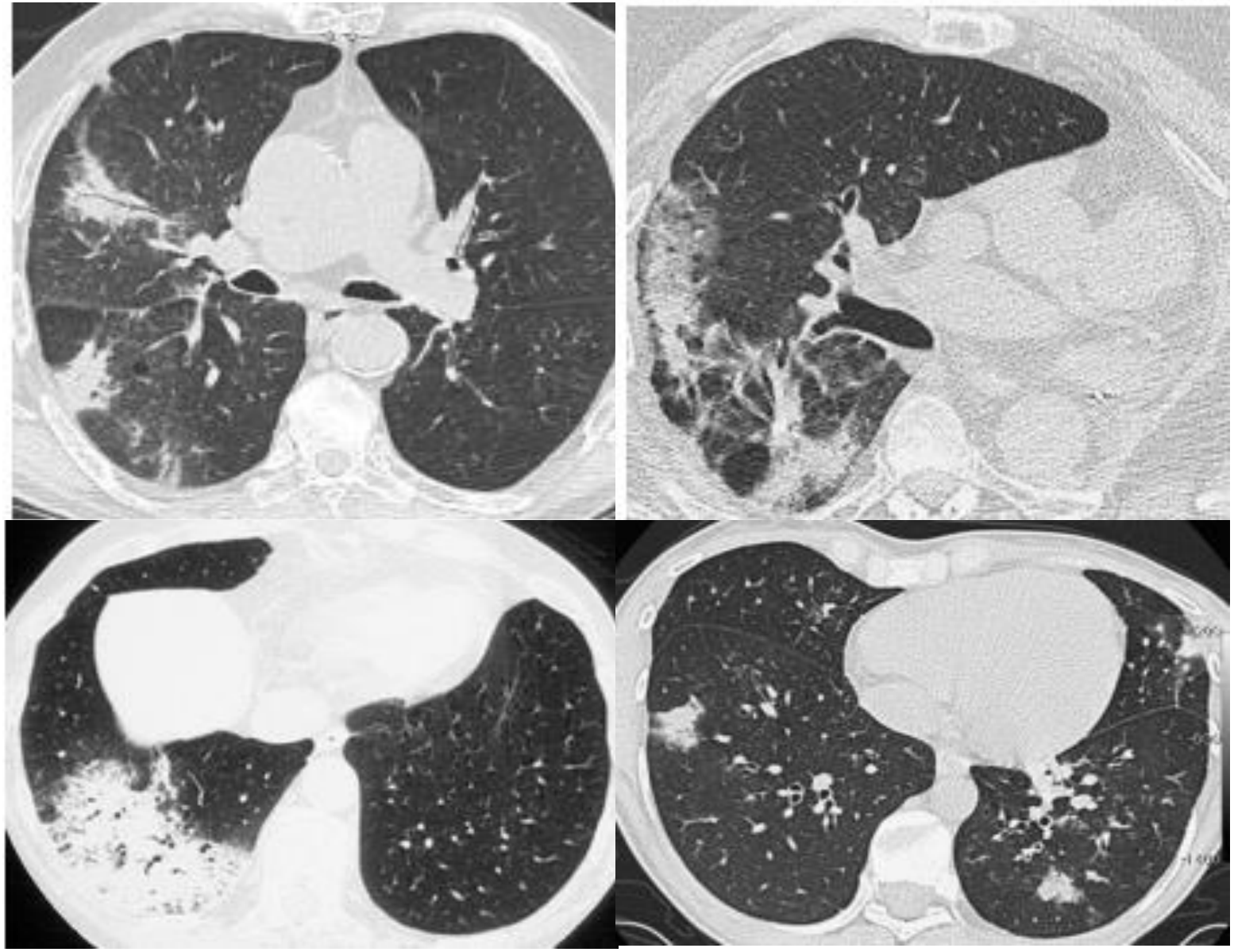
Organizing Pneumonia (OP)



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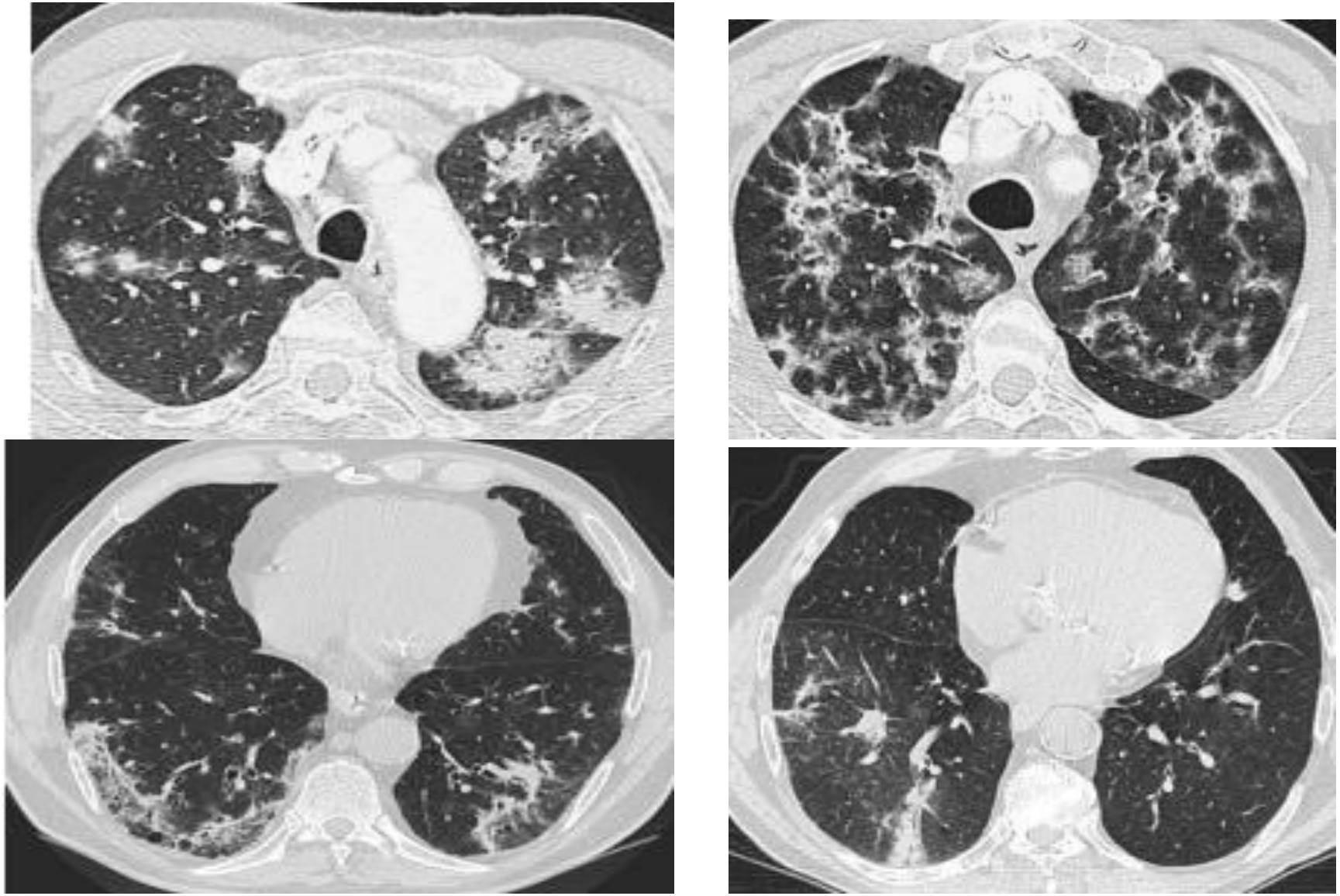
Organizing Pneumonia (OP)



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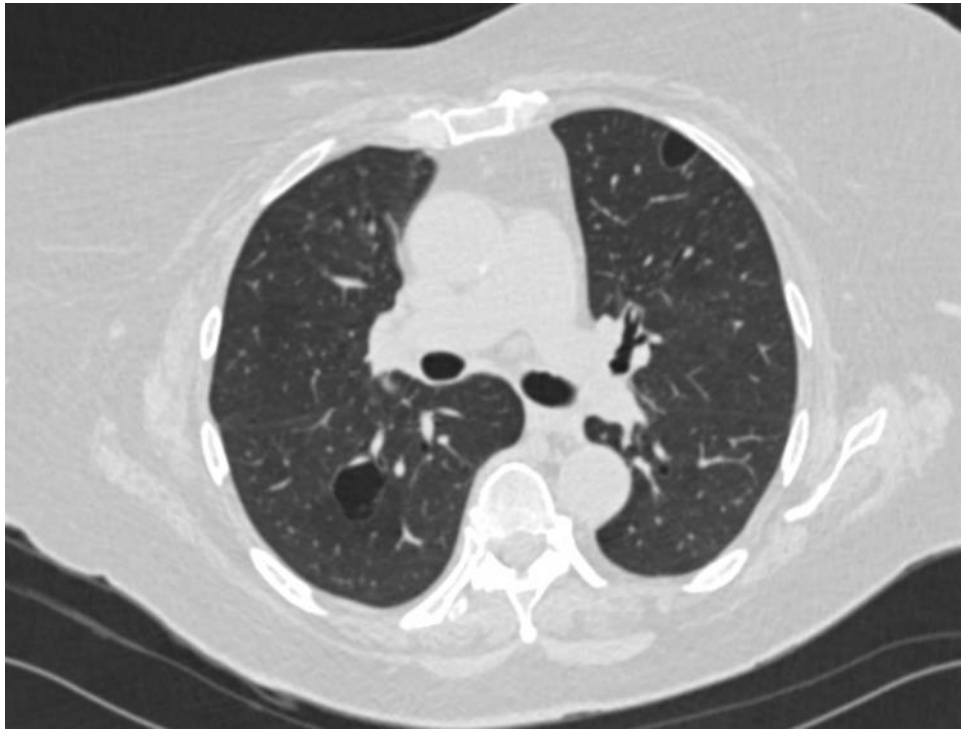
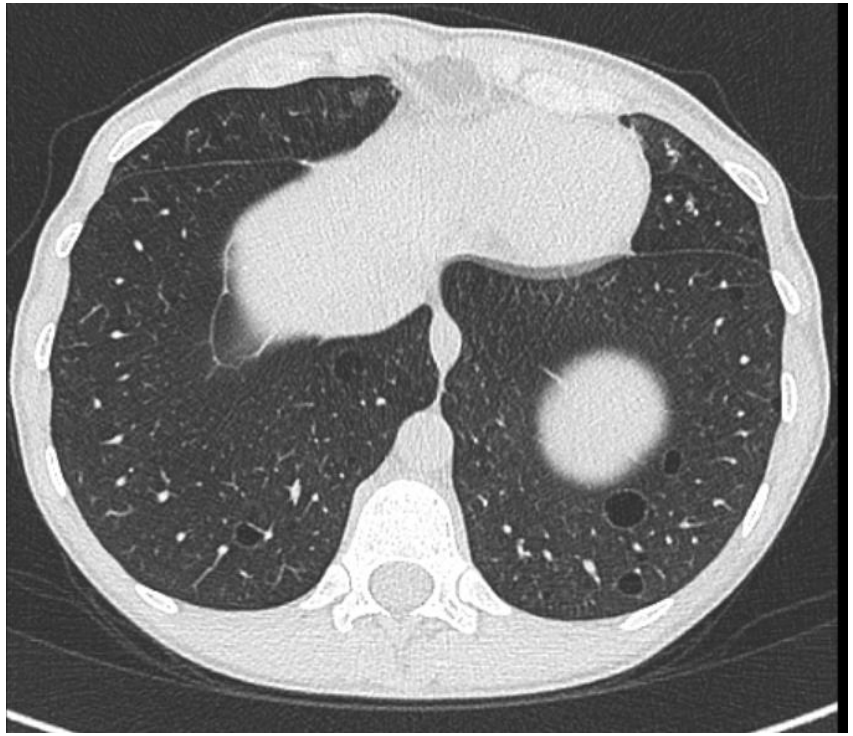
Lymphoid/Lymphocytic Interstitial Pneumonia (LIP)





GGO, nodules and widespread consolidation can be present, thin-walled cysts in 80% of patients, cysts are randomly distributed, involve less than 10% of the lung

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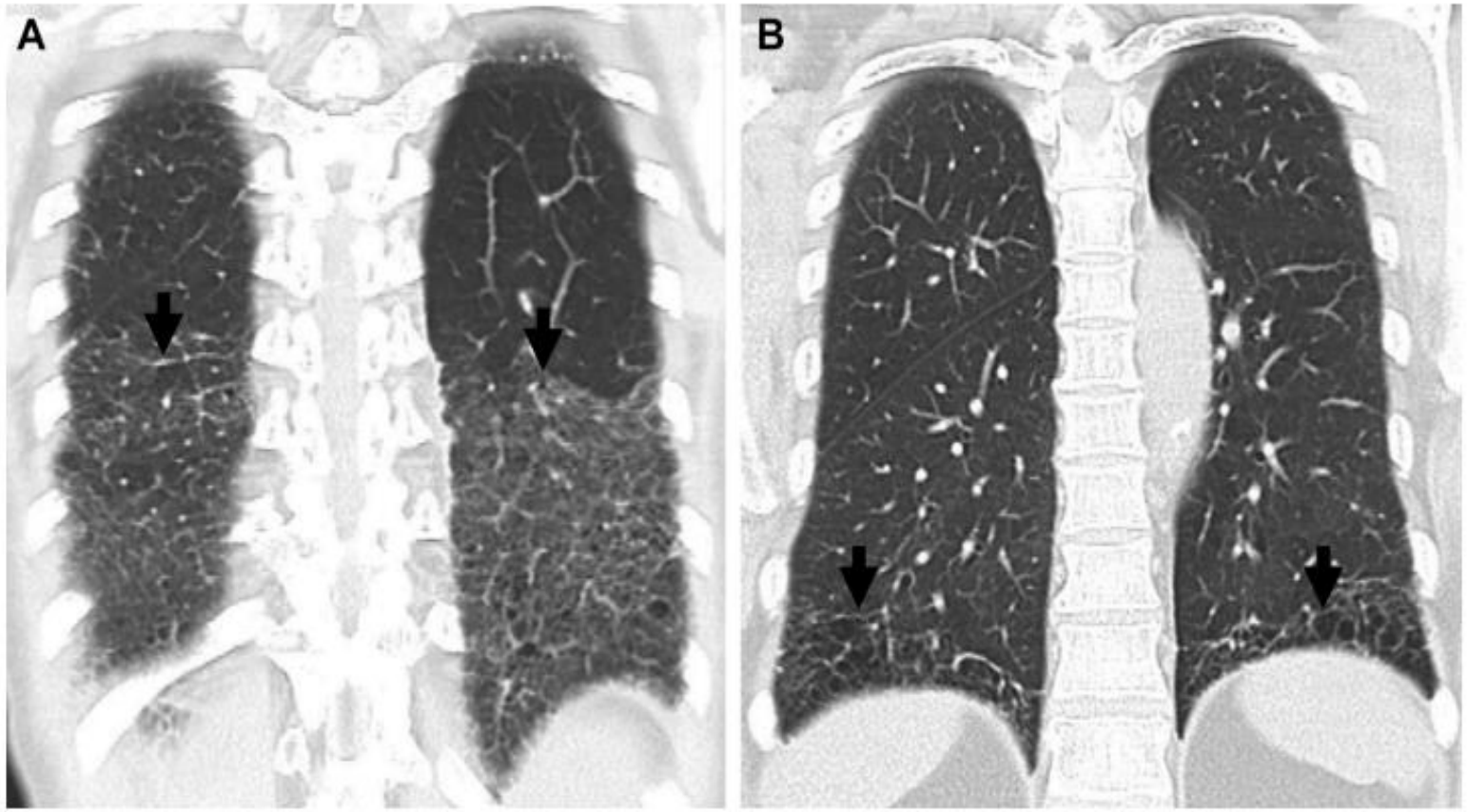
Imaging Features which suggest CTD-ILD



Straight Edge Sign

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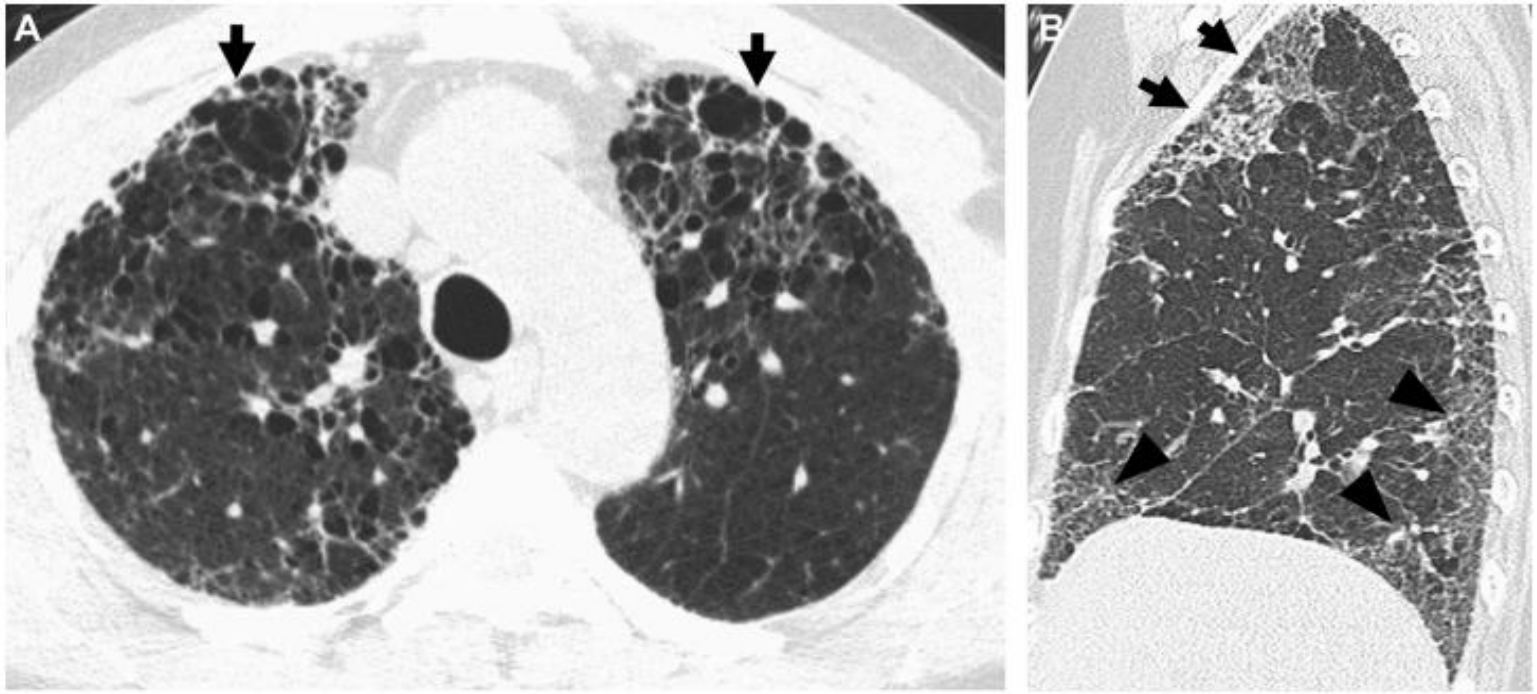
Imaging Features which suggest CTD-ILD



Anterior Upper Lobe Sign

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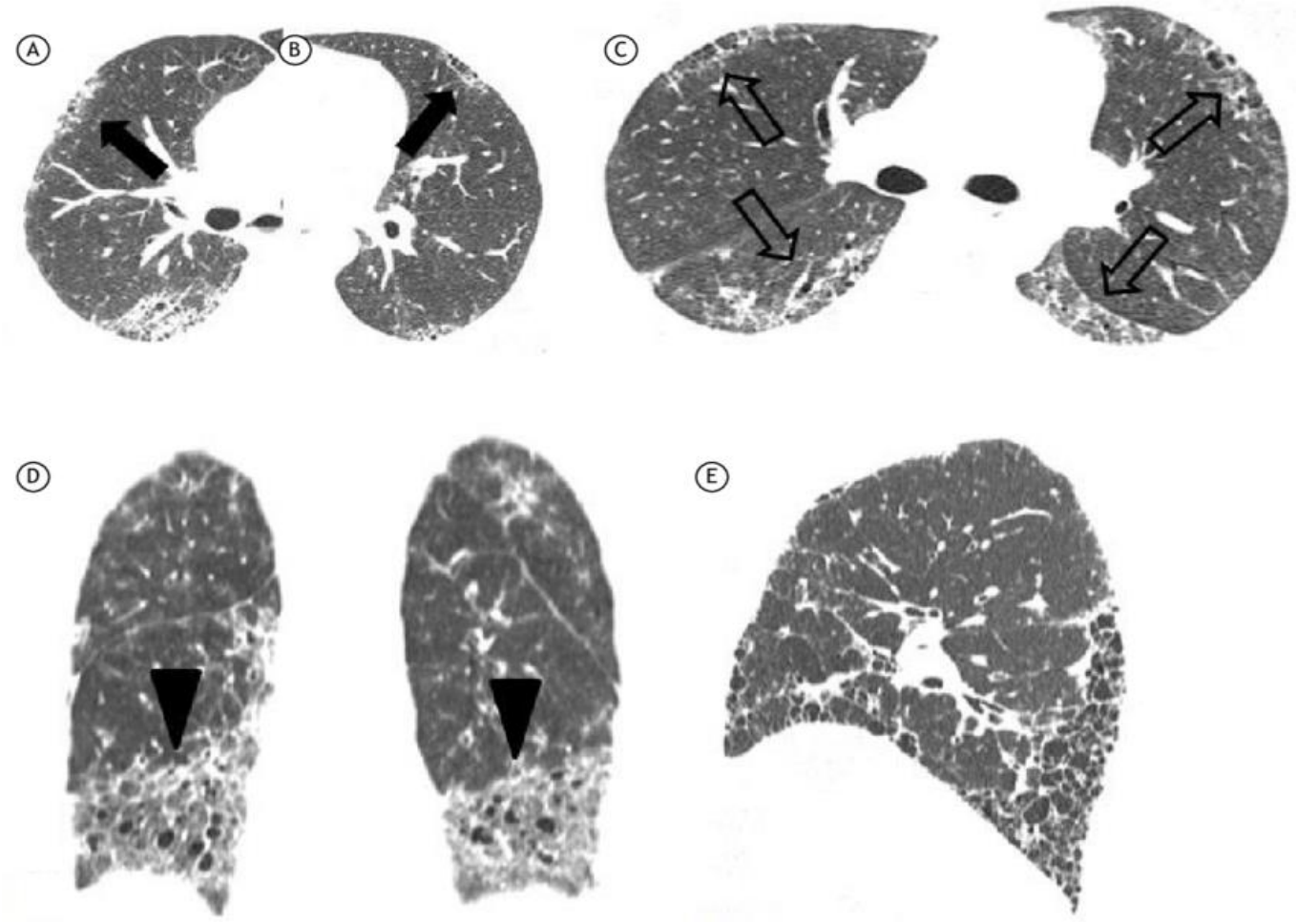
Imaging Features which suggest CTD-ILD



Four Corners Sign

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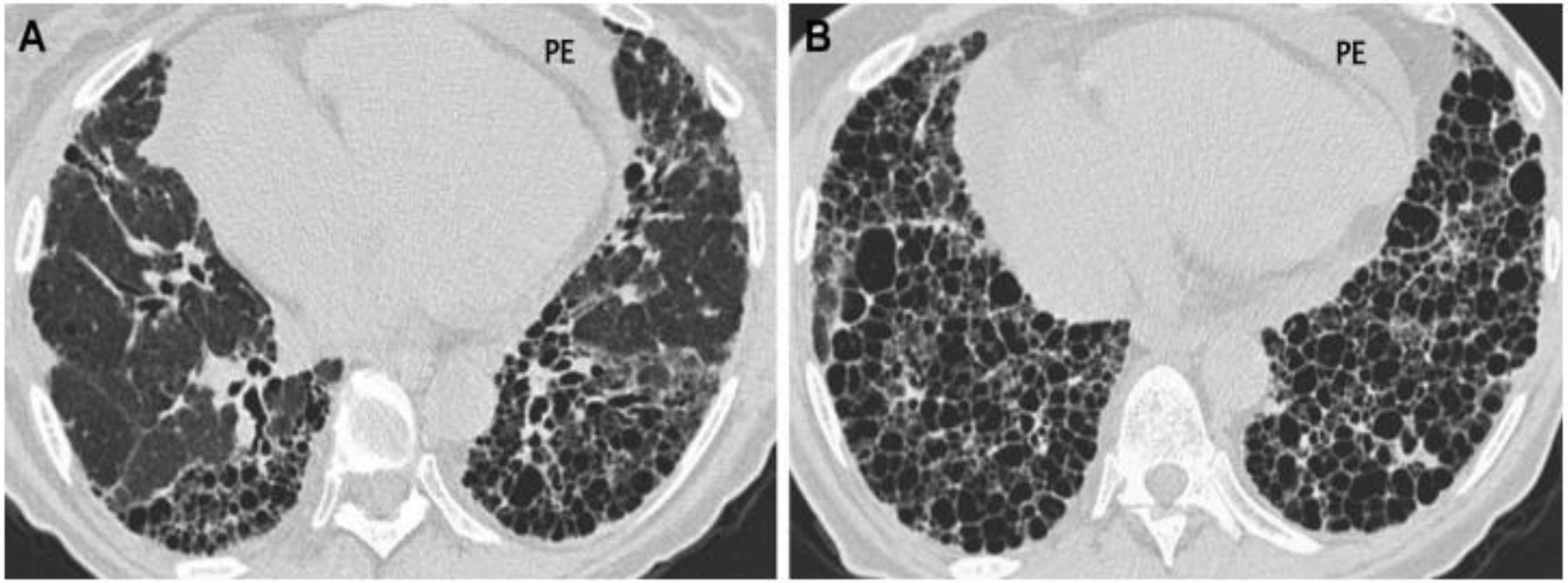
Imaging Features which suggest CTD-ILD



Exuberant Honeycombing

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Epidemiology of IPAF

- Prevalence of IPAF varies between 7 and 34% of all ILDs depending mainly on the population studied and the patient recruitment profile
- Oldham et al (2016) identified 422 patients dx with either IIP or UCTD
  - 34% met IPAF criteria
  - 18% of the IPF cohort met IPAF criteria
- Mean age is 60 to 65 years, with balanced gender
- These characteristics differ from CTD-ILD, where patients are predominantly females and younger
- IPAF patients are more frequently smokers or ex-smokers

Pathophysiology of IPAF

Elusive, as no specific studies have been conducted

It is assumed that pathways involved in IPF and/or in CTD-ILD would be involved in IPAF

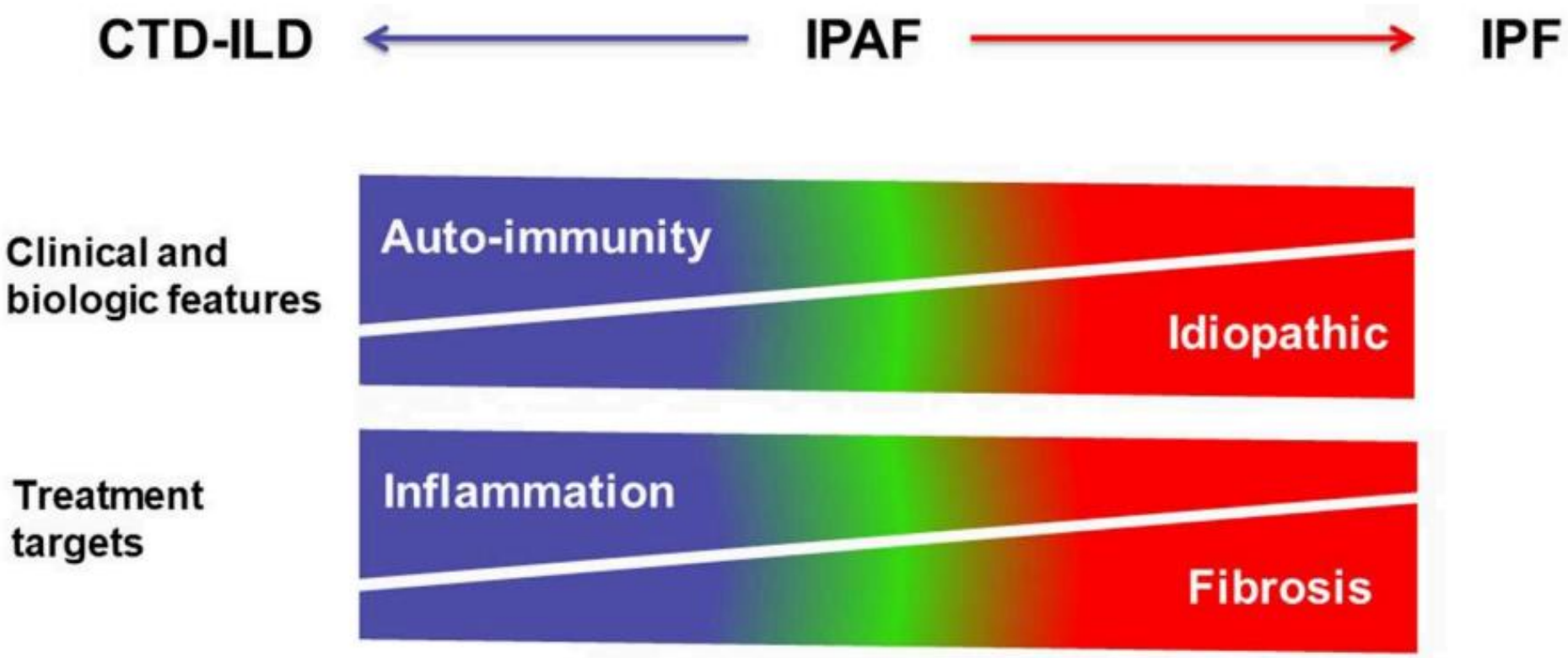
Differences were found between patients with IPAF and those with IPF or CTD-ILD with regard to leukocyte telomere length, MUC5B polymorphism

Management

Unclear whether specific management distinct from that of IPF or CTD-ILD is needed

Pulmonary rehabilitation, long-term oxygen supplementation therapy (if appropriate), and treatment of GERD (if present) are indicated

Pharmacotherapy strategies



Corticosteroids
Immunosuppressants (including MMF/ Azathioprine)

Anti-fibrotics (Nintedanib/Pirfenidone)

Pharmacotherapy strategies

Mycophenolate trended towards reduced decline in FVC and carbon monoxide diffusion capacity in a small cohort of IPAF (*Ther Clin Risk Manag, 2018)*

Nintedanib (OFEV) reduces FVC decline by ~50% in patients with IPF, PPF, and scleroderma (Inpulsis, Inbuild, Senscis trials)

Pirfenidone (Esbriet) reduced FVC decline by ~ 45% in patients with IPF (Ascend trial)

2023 ACR/ACCP Treatment Guidelines for SARD-ILD

	Systemic Sclerosis	Myositis	MCTD	Rheumatoid Arthritis	Sjögren's
First-line ILD therapy — Preferred	Mycophenolate[†] Tocilizumab Rituximab	Mycophenolate[†] Azathioprine Rituximab CNI	Mycophenolate[†] Azathioprine Rituximab	Mycophenolate[†] Azathioprine Rituximab	Mycophenolate[†] Azathioprine Rituximab
First-line ILD therapy — Additional options	Cyclophosphamide Nintedanib Azathioprine	JAKi Cyclophosphamide	Tocilizumab Cyclophosphamide	Cyclophosphamide	Cyclophosphamide
+ Glucocorticoids	**Strong recommendation <u>against</u> GCs**	Short-term GCs[*]	Short-term GCs[*]	Short-term GCs[*]	Short-term GCs[*]

Strong recommendation *against* | Conditional recommendation

Prognosis of IPAF

- Overall, findings suggest that the presence of IPAF criteria is associated with a generally better outcome as compared to IPF, but worse than CTD-ILD
- Among patients classified as IPAF, the UIP pattern at imaging or histopathology may be associated with a more severe outcome as compared to other patterns especially that of NSIP
- One study suggested that patients with non-UIP IPAF pattern had a very similar prognosis to those with CTD-ILD, while disease progression of UIP-IPAF patients resembled that of patients with IPF
- Presence of a clinical domain was associated with a decreased mortality risk
- Presence of a multicompartment feature was a strong predictor of poor outcome

Areas of Uncertainty

10–20% of pts initially classified as IPAF progress to a diagnosis of CTD-ILD

When and how to reevaluate for a connective tissue disease?

Should sicca symptoms, esophageal dysmotility, proximal muscle weakness and myalgia be part of clinical domain?

What is the role of investigations such as nailfold capillaroscopy, salivary gland bx, articular XRAYs and EMG?

Should IPAF criteria be applied differently in UIP patients vs non-UIP?

The Rheumatologist's Role

When to involve rheumatology?

In one study, following rheumatological review, 40% of ILD multi-disciplinary meeting cases received a rheumatology-related ILD dx, including IPAF. One-fifth of IPF diagnoses were reclassified into a CTD-ILD

Take Away Points

- Still debate whether IPAF is a distinct disease entity or overlap of existing conditions
- Significant heterogeneity persists within the group designated by IPAF
- Management may depend on whether specific IPAF case more closely resembles IPF or CTD-ILD
- Reevaluation is necessary as a portion of “IPAF” patients may progress to CTD-ILD at later point
- Rheumatologic evaluation has value in aiding in appropriate classification of ILD

THANK YOU!!!!