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Interstitial Pneumonia with Autoimmune Features (IPAF): A New Classification and a Call for Clarity

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Purpose and Overview:

The field of interstitial lung disease is challenging in many regards. One of the most important distinctions is differentiating idiopathic interstitial pneumonia and interstitial lung disease associated with connective tissue disease. This distinction can be especially difficult as there are a group of patients that have several features of a connective tissue disease but don't meet established diagnostic criteria. These patients occupy a gray zone between the two entities. The purpose of this presentation is to describe a new consensus criteria meant to classify the group of patients that occupy the gray zone between idiopathic interstitial pneumonia and interstitial pneumonia associated with well-defined connective tissue disease. It will start by reviewing the idiopathic interstitial pneumonias and then interstitial pneumonia secondary to connective tissue disease and discuss the importance of distinguishing the two. It will then review earlier attempts to codify the group of patients that don't seem to fit well in either category including the clinical characteristics and available outcomes data. It will then review the recently proposed consensus definition for this group and the proposed criteria. Finally, this presentation will review the justification for the components of the criteria and review the available preliminary data.

Objectives:

1. To understand the importance of distinguishing idiopathic interstitial pneumonia from interstitial pneumonia secondary to connective tissue disease.
2. To describe a group of patients that have features of autoimmunity but do not meet established criteria for a connective tissue disease.
3. To review prior attempts at classifying the patients who have some features of autoimmunity plus interstitial disease.
4. To review the recent joint American Thoracic Society/European Respiratory Society consensus definition and diagnostic criteria for this group of patients.
5. To understand the justifications for the diagnostic criteria chosen.

About the author:

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Abbreviations Key:

ILD – interstitial lung disease

CTD – connective tissue disease

CTD-ILD – interstitial lung disease secondary to connective tissue disease

UCTD – undifferentiated connective tissue disease

UIP – usual interstitial pneumonia

NSIP – non-specific interstitial pneumonia

OP – organizing pneumonia

IPF – idiopathic pulmonary fibrosis (this is the name for idiopathic UIP)

IIP – idiopathic interstitial pneumonia

DIP – desquamative interstitial pneumonia

LIP – lymphocytic interstitial pneumonia

RB-ILD – respiratory bronchiolitis with interstitial lung disease

AIP – acute interstitial pneumonia (previously known as Hamman-Rich syndrome)

IPAF – interstitial pneumonia with autoimmune features

LD-CTD – lung dominant connective tissue disease

RA – rheumatoid arthritis

SSc- scleroderma

PM/DM –polymyositis/dermatomyositis

MCTD – mixed connective tissue disease

SLE – systemic lupus erythematosis

HRCT – high resolution CT of the chest

HP – hypersensitivity pneumonitis

Introduction

Interstitial lung disease (ILD) is a complex group of disorders with approximately 200 different causes. Ninety-five percent of those causes fall into one of the following categories: medication reactions, familial or genetic disease, connective tissue disease, granulomatous disease, occupational/environmental exposures, and idiopathic. The remaining 5% are considered unique entities and will not be discussed further.

The evaluation of patients presenting with ILD focuses on determining the most likely pathologic pattern and excluding known causes. This requires an exhaustive exposure history, family and medication history. One also searches for symptoms or physical exam signs of connective tissue disease and a full laboratory evaluation for autoantibodies is performed. If all of the above is unrevealing then a diagnosis of idiopathic interstitial pneumonia (IIP) becomes most likely.

One of the most important concepts in ILD is that the pathologies listed below are not pathognomonic for idiopathic disease. Every one of those pathologies has multiple potential causes (see table 1). However, some are more likely to be idiopathic than others. For example, the majority of patients with a UIP pattern have idiopathic disease while the opposite is true of NSIP, LIP and OP. As a result, the current gold standard for diagnosis is not biopsy but rather a multidisciplinary discussion between clinicians, thoracic radiologists and thoracic pathologists.

Table 1: Pathologic Patterns and their respective causes

Pathologic Pattern	CTD	Exposure	Drug	Genetic
UIP	RA, Scleroderma, PM/DM Sjogren's	HP (organic antigen, reactive chemicals), asbestos	Macrodantin, amiodarone, chemotherapy, Radiation	Yes
NSIP	Scleroderma, PM/DM, Sjogren's, RA, SLE	HP (organic antigen, reactive chemicals)	Amiodarone, methotrexate, rituximab, chemo	Yes
DIP	RA, SLE	Tobacco, aluminum, cobalt, asbestos, talc	Sirolimus, marijuana, chemotherapy	Yes

Idiopathic Interstitial Pneumonia (IIP)

The IIPs are typically named after their respective pathologic pattern; the only exception is idiopathic pulmonary fibrosis (IPF). IPF is diagnosed when the

underlying pathology is usual interstitial pneumonia (UIP) and all known causes are excluded. The most recent classification system is shown below:

TABLE 1. REVISED AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS: MULTIDISCIPLINARY DIAGNOSES

Major idiopathic interstitial pneumonias
   Idiopathic pulmonary fibrosis
   Idiopathic nonspecific interstitial pneumonia
   Respiratory bronchiolitis–interstitial lung disease
   Desquamative interstitial pneumonia
   Cryptogenic organizing pneumonia
   Acute interstitial pneumonia
Rare idiopathic interstitial pneumonias
   Idiopathic lymphoid interstitial pneumonia
   Idiopathic pleuroparenchymal fibroelastosis
Unclassifiable idiopathic interstitial pneumonias*

(1)

The frequency of each IIP varies by the study but IPF is by far the most common accounting for greater than 50% of the IIPs. In the most recent studies where patients with autoimmune features are excluded, IPF accounts for 70-80% of cases of IIP and idiopathic nonspecific interstitial pneumonia (NSIP) accounts for approximately 10%.(2) The recently described unclassifiable group is likely the second most common IIP accounting for 15-35% of cases depending on the trial.(3) This group of diseases is growing in importance as both the prevalence and mortality rate have increased dramatically over the last 15-20 years.(4, 5)

The prognosis of patients with an IIP depends upon the underlying pathology. IPF has the worst prognosis with an average survival of just over 3 years from the time of diagnosis. This is significantly worse than NSIP where the average survival is greater than 10 years.(6, 7) The unclassifiable group has a worse prognosis than NSIP also but it is not quite as poor as IPF.(3)

The therapy also varies by the pathologic pattern. NSIP, lymphocytic interstitial pneumonia (LIP) and organizing pneumonia (OP) are typically treated with immunosuppressants. In contrast, immunosuppressants are contraindicated in IPF as the recent PANTHER study showed they increase mortality compared to placebo.(8)

Connective tissue disease related interstitial lung disease (CTD-ILD)

Unlike the IIPs, which only affect the interstitium, the various connective tissue diseases can involve virtually any compartment of the respiratory system including the interstitium, the airways, the vasculature, the pleura and the respiratory muscles. The relative frequency with which each compartment is involved varies by the underlying CTD (see table 2). However, involvement of multiple compartments
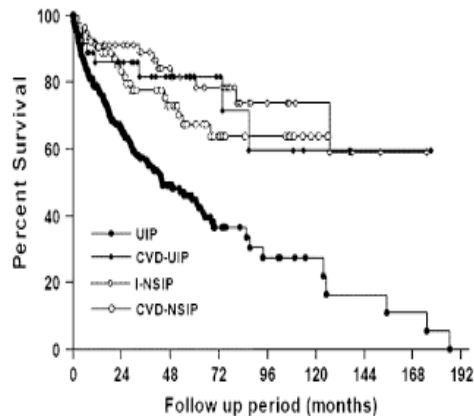
in a single patient is common in CTD-ILD and is one of the distinguishing features from IIP.

Table 2: Pulmonary Complications of CTD(9, 10)

	SSc	RA	Sjogren's	MCTD	PM/DM	SLE
ILD	+++	++	++	++	+++	+
Airways	-	++	++	+	-	+
Pleural	-	++	+	++	+	+++
Vascular	+++	+	+	++	+	+
Hemorrhage	-	+	-	-	-	++

A variety of pathologic subtypes occur in CTD-ILD including NSIP, UIP, OP, LIP, AIP and rarely DIP. The relative frequency of each pathologic pattern also varies by the underlying CTD. Overall, NSIP is the most frequent pathologic pattern and it is the most frequent pathology found in all of the above CTDs except for rheumatoid arthritis (RA). UIP is the most common underlying pathology in RA associated ILD accounting for 55-60% of cases. The frequency of clinically significant interstitial disease varies by the underlying CTD as well ranging from a high of 80% in scleroderma to 5-15% in RA. According to the American Thoracic Society guidelines diagnosing a CTD-ILD requires a patient meet American College of Rheumatology criteria for an underlying CTD, the presence of ILD and exclusion of other known causes of ILD like medication reactions and inhalational exposures.(1)

We have known for quite some time that patients with ILD secondary to a connective tissue disease have a better prognosis than those with IIP. However, the fact that NSIP is the most common underlying pathology in CTD-ILD only became apparent in the last 15 years. As idiopathic NSIP has a better prognosis than IPF this raises the possibility that the improved prognosis in CTD is simply a result of the difference in the dominant pathologic pattern. Studies over the last 8 years have answered that question. The most frequently cited study is by Park et al who studied several hundred patients all of whom had surgical lung biopsy. Their data clearly showed that patients with UIP secondary to CTD have a markedly better prognosis than IPF. In addition, their data showed that the pathologic pattern did not influence prognosis in CTD-ILD (see figure).(11) In that study, idiopathic NSIP

had a similar prognosis to CTD-ILD; however, most other studies show that CTD-ILD related NSIP has a better prognosis than idiopathic NSIP.(12) Additional studies have since confirmed UIP secondary to CTD has a significantly better prognosis than IPF.(13, 14) The only possible exception is UIP secondary to RA. Some studies show a similar prognosis for IPF and RA-UIP. Others show that RA-UIP has a better outcome than IPF but confirm a worse prognosis than UIP associated with other CTDs.(14, 15)

There is very limited clinical trials data to guide therapy of CTD-ILD and virtually all of the existing data is in ILD associated with scleroderma. The 2 multicenter randomized controlled trials available compared Cytoxan to placebo and found that treated patients tended to stabilize or improve slightly while the untreated patients continued to progress.(16, 17) The absence of marked improvement is not surprising as the available therapies cannot reverse fibrosis and most scleroderma patients have fibrotic NSIP. Cytoxan, by limiting the immune mediated lung injury, thus helps prevent lying down of additional scar. The best available data for the other CTD-ILDs is a retrospective cohort trial of mycophenolate mofetil that showed the PFT trend was to decline prior to initiation followed by slow gradual improvement on therapy.(18) A follow-up double blind randomized placebo controlled multicenter trial in scleroderma ILD comparing mycophenolate and cyclophosphamide was recently completed but the results are not yet published. The current standard of care for CTD-ILD is thus therapy with a combination of prednisone and a steroid sparing agent, typically mycophenolate, azathioprine or cyclophosphamide.

CTD-ILD versus IIP

The above discussion highlights several important differences between IIP and CTD-ILD. First, the prognosis is clearly different and finding an underlying CTD identifies a patient with a vastly better prognosis. In addition, the evaluation of ILD in a CTD patient is different than in IIP. Since the underlying pathology does not affect prognosis or therapy in CTD, surgical lung biopsy to define the pathologic pattern is rarely employed. In contrast, surgical lung biopsy is required in the majority of patients with IIP because less invasive biopsies do not provide an adequate sample for diagnosis and the HRCT findings are only specific enough in a minority of patients. A surgical lung biopsy is thus necessary to define the pathologic pattern in

order to guide therapeutic decisions and discussions about prognosis in patients with an IIP. Finally, the therapeutic standard of care for CTD-ILD is contraindicated in IPF, which accounts for the majority of IIP patients. It is thus critically important to differentiate the two conditions.

Case Study

KP is a 48 year old woman with a past history of fibromyalgia, gastroesophageal reflux and hypertension who presents with 5 years of cough and more recently mild exertional dyspnea. Interstitial changes were discovered after she had an abdominal CT to evaluate abdominal pain. A subsequent high-resolution chest CT confirmed ILD in a pattern most consistent with fibrotic NSIP. Her review of systems was significant for puffy fingers, Raynaud's, prolonged morning stiffness in her hands, and a malar photosensitive rash. Her exam revealed puffy fingers, Raynaud's and crackles. Her lung function had moderate restriction and a severely reduced DLCO. As the DLCO was lower than expected for the amount of interstitial disease on her HRCT an echocardiogram was obtained and suggested pulmonary hypertension. A cardiac catheterization then confirmed severe pulmonary arterial hypertension, group 1. Her autoimmune serologies showed an ANA of 1:1280 but her ENA, RF, CCP, Ds-DNA, anti-centromere antibody and an extended myositis profile were negative.

This case illustrates a frequent clinical problem. She has several features of autoimmune disease including Raynaud's, prolonged morning stiffness, puffy fingers, photosensitive rash, multicompartment pulmonary involvement (interstitium and vasculature) and a markedly elevated ANA. Despite this, she does not meet criteria for a defined connective tissue disease. She comes closest to scleroderma but only has 7 of the 9 points required for diagnosis.{van den Hoogen, 2013 #65} She occupies what I will refer to as a gray zone between IIP and CTD-ILD. Does she have a prognosis similar to one or the other or is her prognosis something in between? Will she respond to immunosuppressants like CTD-ILD or should she have a biopsy to exclude UIP? Other patients have fewer features but still some that suggest autoimmunity. If there is a difference between the gray zone patients and IIP/CTD-ILD patients where should the line defining the gray zone be drawn? These are unanswered questions but over the last 8 years several groups of investigators have attempted to classify and study this group of patients in order to obtain answers.
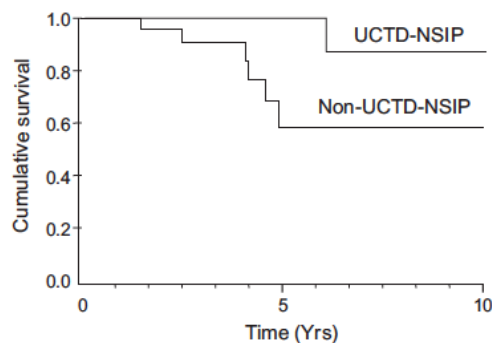
Kinder et al. and UCTD

The first attempt to classify the patients in the gray zone was published by Kinder et al in 2007.(19) They used the term undifferentiated connective tissue disease to refer to ILD patients in the gray zone and their diagnostic criteria are shown below. They found that 37% of the patients previously classified as IIP met their proposed diagnostic criteria. The patients that satisfied the criteria were younger, more likely to be female and NSIP was the most frequent suspected pathology. Eighty seven percent of patients with biopsy confirmed NSIP satisfied the criteria. This led the

authors to propose that NSIP itself is a manifestation of autoimmunity. In a follow-up study they showed that the patients who met their criteria had better outcomes than IPF.(20) This was criticized due to the known prognostic difference between IPF and NSIP. However, other investigators testing different patient populations showed a

TABLE 1. DIAGNOSTIC CRITERIA FOR PATIENTS WITH UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE*

Diagnostic Criteria	Presence of
Symptoms associated with connective tissue disease	At least one of the following symptoms: 1. Raynaud's phenomenon 2. Arthralgias/multiple joint swelling 3. Photosensitivity 4. Unintentional weight loss 5. Morning stiffness 6. Dry mouth or dry eyes (sicca features) 7. Dysphagia 8. Recurrent unexplained fever 9. Gastroesophageal reflux 10. Skin changes (rash) 11. Oral ulceration 12. Nonandrogenic alopecia 13. Proximal muscle weakness
Evidence of systemic inflammation in the absence of infection	Positive findings for at least one of the following: 1. Antinuclear antigen 2. Rheumatoid factor 3. Anti–SCL 70 antibody 4. SS-A or SS-B 5. Jo-1 antibody, 6. Sedimentation rate (> two times normal), C-reactive protein

significantly better prognosis than idiopathic NSIP if the proposed criteria are satisfied (see below).(12, 21) These trials also showed UCTD patients were younger and more likely to be female. However, the frequency with which NSIP patients satisfied the above criteria was much lower, 38% and 46%, respectively.

However, when the Kinder criteria were applied to a population whose pathology was UIP (by CT or biopsy) there was no difference in outcome between UCTD-UIP and IPF.(22)

The Kinder label and criteria have both been criticized. Rheumatologists use the term undifferentiated connective tissue disease to refer to a group of patients with symptoms and serology consistent with autoimmunity but who don't meet ACR criteria. They have minimal visceral involvement and tend to follow a benign course. The patients in the Kinder study had visceral involvement by definition and a

significant percentage do not have a benign course, as described above. In addition, the specificity of the criteria is questionable. For example, a 60 year old man with GERD and an ANA of 1:40 would be defined as UCTD. Studies have previously shown that over 20% of normal individuals will have an ANA positive in that range and a similar percentage of patients in that age range have GERD.(23) There is thus a significant chance for misclassification with these criteria.

Other proposed criteria and names

Several other investigators have proposed different criteria and names to address these problems. All of these studies were retrospective cohort trials similar to Kinder using the ILD populations at each respective center. These criteria are summarized in the table below.(24) Vij et al. used the term autoimmune featured interstitial lung disease (AIF-ILD) and proposed criteria similar to Kinder but added some more specific antibodies and changed the ANA cutoff of to greater than or equal to 1:160.(25)

Table 1
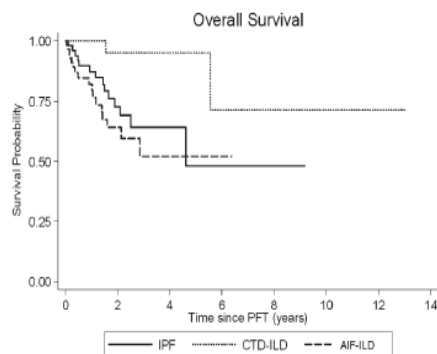Four criteria for interstitial pneumonia with features of autoimmune disease.

A. Presence of interstitial lung disease (all criteria)			
B. Absence of other underlying cause for lung disease, including a defined connective tissue disease (all criteria)			
C. Clinical criteria (at least one of the following)			
Kinder criteria [4]	Vij criteria [5]	Corte criteria [6]	Fischer criteria [7]
Raynaud's	Raynaud's	Raynaud's	None required
Arthralgia/multiple joint swelling	Arthralgia/joint swelling	Arthralgia/joint swelling	
Morning stiffness	Morning stiffness	Morning stiffness	
Sicca	Sicca	Sicca	
Proximal muscle weakness	Proximal muscle weakness	Proximal muscle weakness	
Photosensitivity	Photosensitivity		
Weight loss	Weight loss		
Dysphagia	Dysphagia		
Gastroesophageal reflux	Gastroesophageal reflux		
Skin changes/rash	Rash		
Oral ulcers	Oral ulcers		
Recurrent fevers	Hand ulcers		
Alopecia (non-androgenic)	Leg or foot swelling		
D. Serologic criteria (at least one positive serology of the following)			
Kinder criteria	Vij criteria	Corte criteria	Fischer criteria
ANA (any titer)	ANA ≥ 1:160	ANA (high titer)	ANA > 1:320
RF (any titer)	RF (any titer)	RF (high titer)	RF (>60)
Anti-Scl-70	Anti-Scl-70	Anti-Scl-70	Anti-Scl-70
Anti-Ro (SSA)	Anti-Ro (SSA)	Anti-Ro (SSA)	Anti-Ro (SSA)
Anti-La (SSB)	Anti-La (SSB)	Anti-La (SSB)	Anti-La (SSB)
Anti-Jo1	Anti-Jo1	Anti-Jo1	Anti-Jo1 or other anti-tRNA
ESR or CRP >2x normal	ANCA	Anti-Centromere	Anti-RNP
	Anti-RNP	Anti-RNP	Anti-Smith
	Anti-Smith	Anti-Smith	Anti-CCP
	Anti-CCP		Anti-ds-DNA
	Anti-ds-DNA		
	Elevated aldolase		
	Elevated CK		
E. Pathologic criteria (Fischer criteria only: instead of a positive serology, presence of two or more of the following on histopathology)			
Lymphoid aggregates with germinal centers			
Extensive pleuritis			
Prominent plasmacytic infiltrates			
Dense perivascular collagen			

Abbreviations: ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; CCP, cyclic citrullinated peptide; CK, creatinine kinase; CRP, C-reactive protein; ds-DNA, double-stranded deoxyribonucleic acid; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; RNP, ribonucleoprotein; tRNA, transfer ribonucleic acid.

Corte et al. used the term UCTD but proposed much stricter criteria with an ANA cutoff of greater than or equal to 1:320 and an RF of two times normal and they limited their clinical findings to things more strongly associated with CTD.(26) Fischer et al proposed a set of criteria but didn't apply it to their ILD population. They proposed the term lung-dominant CTD (LD-CTD).(27) Their criteria did not
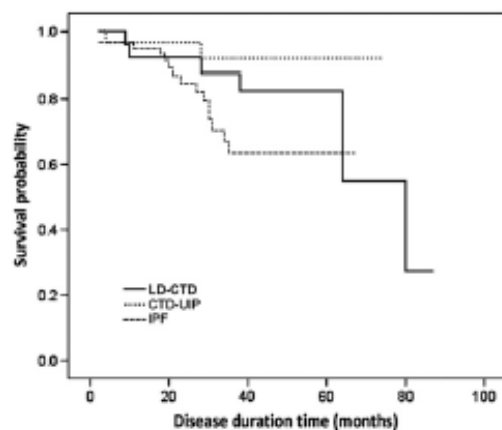
require and signs or symptoms but focused instead on more specific serologies and added certain pathologic criteria thought to be more common in CTD-ILD than IIP.

Not surprisingly, the results vary in each of these studies. However, all of them found that patients that met their proposed definitions were younger and more likely to be female. Vij et al. found that 50% of their IIP patients satisfied the criteria they proposed. Unlike the Kinder trial, UIP was the most frequent pathologic pattern accounting for 62% of cases. Overall there was no difference in survival between those they called autoimmune featured ILD and IPF as shown below.

Overall Survival

However, they did show that each titer increase in ANA had a hazard ratio for mortality of 0.81 (0.67-0.99) and when the ANA was at least 1:1280 survival was improved in the autoimmune featured group.(25)
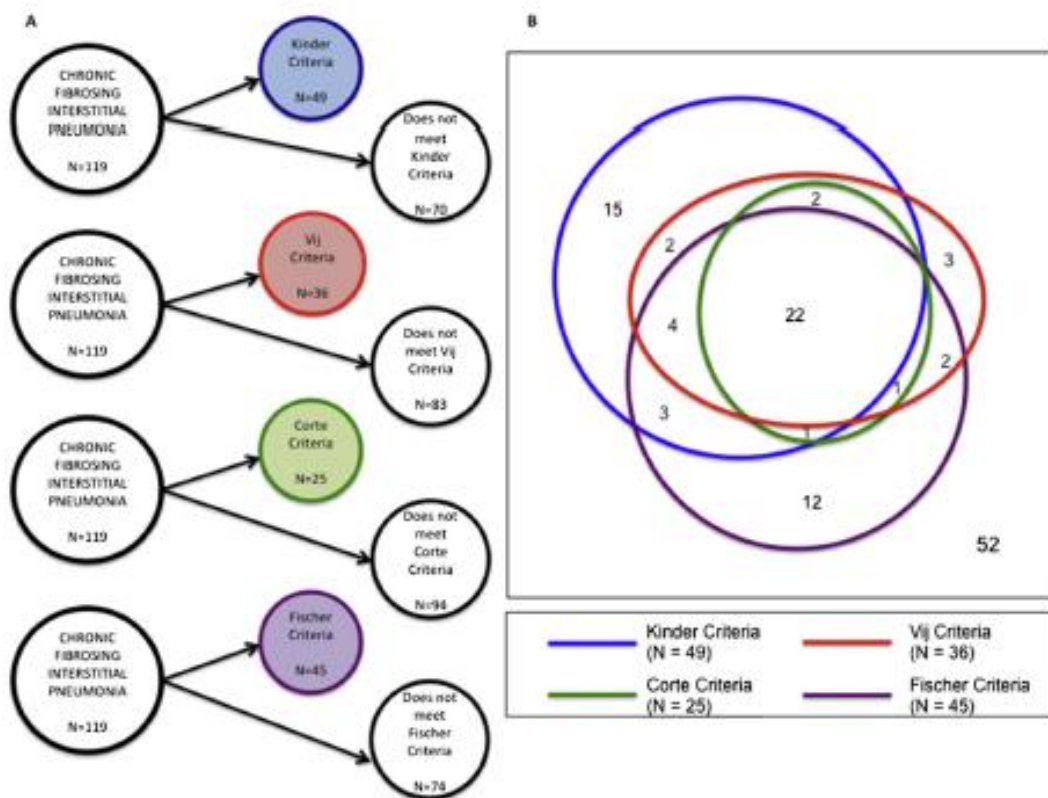
Fischer did not apply their proposed criteria to their own population. However, another group did apply them to a group of 118 consecutively diagnosed UIP patients.(28) They found that CTD and lung dominant CTD (LD-CTD), as proposed by Fischer, each accounted for 15% of the patients and the remainder had IPF. Clinically, the LD-CTD patients resembled the CTD patients.

The survival of curve of the LD-CTD group appears to be somewhere between the two well- characterized groups but given the small numbers statistical significance was not achieved.

Corte et al. applied their criteria to a group of 101 patients with biopsy proven NSIP or UIP.(26) 21% of the total met the definition they proposed and 2/3 of those had NSIP. In this study, 31% of the patients with NSIP and 13% of those with UIP met their proposed criteria. They also did not find a difference in survival between the groups. However, two other investigators also looked at the Corte criteria compared to idiopathic disease. Moua et al from the Mayo clinic restricted their analysis to those with UIP. They had a much larger sample size and found a statistically significant improvement in survival versus IPF if Corte's definition for UCTD was met. In fact the UCTD patients in this trial had similar outcomes to the other CTDs, excluding RA, and better outcomes than those with RA.(29)

Assayag et al from UCSF identified 119 patients with either UIP or NSIP diagnosed between 2005 and 2010. They applied all 4 of the above sets of criteria to the same population. They found a statistical trend to improvement in survival with all of the criteria on univariate analysis. However, on multivariate analysis only the Corte criteria achieved a statistically significant improvement in mortality compared to idiopathic disease.(24) They also found relatively wide variability in the percent of patients meeting the various criteria and incomplete overlap as shown below:(24)

Summary of previously proposed criteria

In summary, the above criteria all show that a significant fraction of the patients that are classified as idiopathic according to current guidelines have an autoimmune flavor, or to put it another way, occupy the gray zone between IIP and CTD-ILD.

These patients tend to be younger and are more likely to be female. However, the varying definitions limit our ability to interpret the existing data. As a result, the relevance of the gray zone to outcome is unclear. Thus far it appears that the pathologic pattern may affect prognosis as in IIP. NSIP patients that meet the broader definition appear to have a better prognosis than those with idiopathic disease but UIP patients do not. In contrast, UIP patients meeting the most specific of the available definitions appear to have a better prognosis. Whether or not this is due to a difference in the effects of immunosuppressants in this population or to the underlying disease is unknown. In addition, the existing data is hampered by the referral bias inherent in all these single center retrospective studies. Larger multicenter trials are required to answer the questions surrounding this group of patients but our ability to conduct those trials is limited by the absence of a consensus definition.

Interstitial Pneumonia with Autoimmune Features (IPAF)

The American Thoracic Society thus worked with the European Respiratory Society to develop a consensus label (above) and set of diagnostic criteria.(30) The committee included representatives from all the above sites plus additional pulmonologists and rheumatologists with expertise in the area and their goal was to develop a uniform name and classification criteria to serve as a platform for future research. Their criteria are below (see next page).(30)

They divided the criteria into 3 domains; clinical, serologic and morphologic. To qualify for an IPAF designation the patient must have ILD by HRCT or surgical lung biopsy. Known alternative etiologies including genetic lung disease, ILD secondary to medication or occupational/environmental exposures have to be excluded. In addition the patient cannot meet established criteria for a defined connective tissue disease. They then have to have one feature from at least two of the proposed domains. This morphologic domain can by defined by a suggestive radiology pattern by HRCT or by biopsy. The reason is that CT can be highly suggestive or actually diagnostic of the underlying pathology if certain features are seen. Additional supplemental pathology findings that satisfy the criteria for patient with UIP (they aren't necessary for NSIP, OP or LIP) include lymphoid aggregates with germinal centers and diffuse lymphoplasmacytic infiltration. The reasons for that will be discussed below. Finally, multi-compartment involvement satisfies the criteria for the morphologic domain for the reasons described above. These include any of the following in addition to the interstitial pneumonia: pleural or pericardial disease, unexplained intrinsic airways disease or unexplained pulmonary vascular involvement.

TABLE 1 Classification criteria for "interstitial pneumonia with autoimmune features"

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) *and*,
2. Exclusion of alternative aetiologies *and*,
3. Does not meet criteria of a defined connective tissue disease *and*,
4. At least one feature from at least two of these domains:
    A. Clinical domain
    B. Serologic domain
    C. Morphologic domain

A. Clinical domain
    1. Distal digital fissuring (*i.e.* "mechanic hands")
    2. Distal digital tip ulceration
    3. Inflammatory arthritis *or* polyarticular morning joint stiffness ⩾60 min
    4. Palmar telangiectasia
    5. Raynaud's phenomenon
    6. Unexplained digital oedema
    7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

B. Serologic domain
    1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns *or*
        a. ANA nucleolar pattern (any titre) *or*
        b. ANA centromere pattern (any titre)
    2. Rheumatoid factor ⩾2× upper limit of normal
    3. Anti-CCP
    4. Anti-dsDNA
    5. Anti-Ro (SS-A)
    6. Anti-La (SS-B)
    7. Anti-ribonucleoprotein
    8. Anti-Smith
    9. Anti-topoisomerase (Scl-70)
    10. Anti-tRNA synthetase (*e.g.* Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
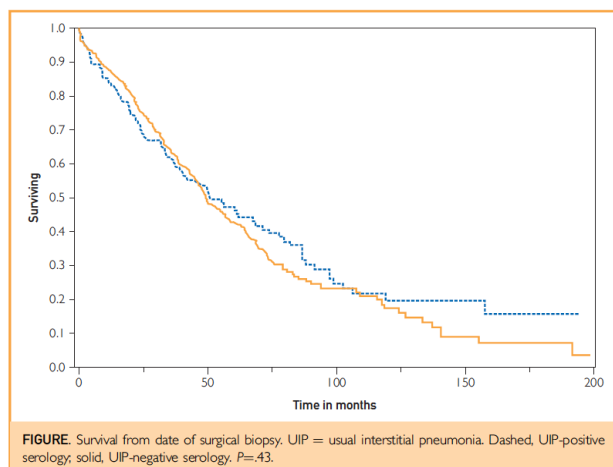   11. Anti-PM-Scl
    12. Anti-MDA-5

C. Morphologic domain
    1. Suggestive radiology patterns by HRCT (see text for descriptions):
        a. NSIP
        b. OP
        c. NSIP with OP overlap
        d. LIP
    2. Histopathology patterns or features by surgical lung biopsy:
        a. NSIP
        b. OP
        c. NSIP with OP overlap
        d. LIP
        e. Interstitial lymphoid aggregates with germinal centres
        f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
    3. Multi-compartment involvement (in addition to interstitial pneumonia):
        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

(30)

Justifications

The importance of including a clinical domain is demonstrated by several studies that show positive serology alone does not alter prognosis in patients with UIP.

FIGURE. Survival from date of surgical biopsy. UIP = usual interstitial pneumonia. Dashed, UIP-positive serology; solid, UIP-negative serology. P=.43.

The largest trial was from the Mayo clinic and results are shown.(31) Similar findings were found in two other cohorts, one from Korea and the other from San Franciso.(13, 32) It is important to realize that most of the data in these trials is driven by ANA positivity at titers lower than the proposed 1:320 cutoff let alone the 1:1280 cutoff in the Vij trial that was associated with improved outcomes. Larger multicenter trials are required to exclude an effect of those titers or positivity in the more specific antibodies on prognosis.

Other studies show that rash, prolonged morning stiffness and Raynaud's are very uncommon in IPF but occur in a significant minority of patients meeting one of the above definitions.(19, 33) Importantly, there was no statistically significant difference in these manifestations between patients with well-defined CTD and

	a	b	c			
	UCTD[e]	IPAF	U-ILD	a vs c	a vs b	b vs c
	Pts no. 52	Pts no. 35	Pts no. 15	p	p	p
Demographic features						
Females % (F/M)	86% (44/8)	69% (24/11)	60% (9/6)	ns	ns	ns
Pts mean age (yrs SD)[b]	55 ± 13	63 ± 12	68 ± 8.9	0.001	ns	ns
Disease dur (mean yrs SD)[a]	12.1 ± 8.4	7.1 ± 3.1	5.3 ± 2.6	0.003	0.009	ns
Follow-up (mean yrs SD)	6.1 ± 4.4	3.9 ± 2.9	3.5 ± 2.2	0.027	0.019	ns
Clinical features						
Arthralgias	91.4%	66.7%	57.1%	0.05	0.04	ns
Arthritis	34.3%	12.9%	0%	0.009	ns	ns
Morning stiffness	40%	17.8%	0%	0.004	ns	ns
Puffy fingers	0%	0%	0%	ns	ns	ns
Myalgias	20%	40.6%	30.4%	ns	ns	ns
Proximal muscle weakness	0%	0%	0%	ns	ns	ns
Rash	54.3%	23.3%	0%	≤0.001	0.02	ns
Phosensitivity	37.1%	3.7%	0%	0.005	≤0.001	ns
Alopecia	2.9%	0.0%	0%	ns	ns	ns
Dermatitis	2.9%	3.6%	0%	ns	ns	ns
Mechanics' hand	0%	0%	0%	ns	ns	ns
Gottron's sign	0%	0%	0%	ns	ns	ns
Skin ulcers	2.9%	0%	0%	ns	ns	ns
Oral ulceration	5.7%	0%	0%	ns	ns	ns
Oral dryness	62.9%	48.2%	40%	ns	ns	ns
Ocular dryness	65.7%	45.2%	25%	0.01	ns	ns
Dysphagia	19.4%	0%	0%	ns	0.01	ns
Recurrent fever[c]	10.3%	0%	0%	ns	ns	ns
Weight loss	3.6%	2.9%	6.7%	ns	ns	ns
Raynaud's phen.	77.1%	66.7%	0.0%	≤0.001	ns	≤0.001
Serositis	14.3%	15.4%	6.7%	ns	ns	ns

those in the gray zone. Most recently, a group from France applied the IPAF definition to their population and compared it to IIP (called U-ILD in the table below).(34) As the table above shows, arthralgias

are common in IIP. However, arthritis and morning stiffness are not. The same is true of Raynaud's and rash in general. The clinical features included in the IPAF definition thus appear reasonable and necessary.
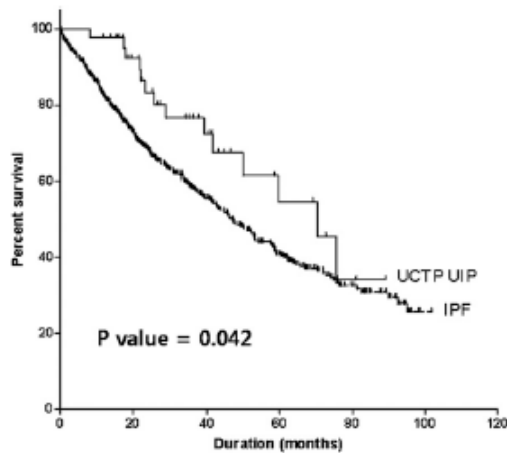
As noted above any positive ANA is not reasonable, as it will capture a large percentage of normal individuals. The question thus becomes is there an appropriate cutoff. Studies have shown that an ANA of 1:320 occurs in 3% or less of normal individuals and the studies cited above show that the same is true in IPF.(32) In contrast, patients in the gray zone have an ANA greater than or equal to 1:320 between 40-80% of the time.(25, 34, 35) The ANA cutoff chosen thus appears to be a reasonable way to separate the populations. There is not enough data available to comment on the RF or the more specific antibodies, as the numbers are too small. However, all were uncommon in the IPF patients in all the above studies. Most were present in 3% or less. The only exceptions were the RNP and the SSA that were present in between 5-10% of IPF patients. In addition, there were significantly more ENA positive patients in the IPAF group than the IIP group in the Ferri trial.(34)

Several features in the morphologic domain deserve comment. First, is the use of NSIP, OP and LIP to satisfy the criteria. This is related to their relative frequencies. The vast majority of patients with LIP have Sjogren's disease. NSIP is more often than not secondary to a known cause.(7) CTD is one of the more common causes of NSIP and the same is true of OP. NSIP is the also most common underlying pathology in CTD and NSIP overlapping with OP is virtually always found in CTD. The presence of any of the above pathologies thus increases the pretest probability that the patient in question has a CTD. In contrast, UIP is more often than not idiopathic so its presence alone does not increase the pretest probability of an underlying CTD and it does not satisfy the morphologic criteria. However, certain accessory findings in UIP should increase one's suspicion. For example multicompartment involvement defined as interstitial involvement plus serosal, airway or vascular disease, does not occur in IIP and is common in CTD. This explains its inclusion in the IPAF criteria. The IPAF criteria also include interstitial lymphoid aggregates with germinal centers or diffuse lymphoplasmacytic infiltration. The data for those come from two sources. First, it is well known that the lung involvement precedes the onset of the connective tissues disease in a minority of patients, about 5-15% depending on the CTD involved. A pathologic predictor for the subsequent development of a full-blown CTD is the presence of lymphoid aggregates with germinal centers.(36) Lymphoid aggregates with germinal centers are also significantly more common in UIP secondary to CTD than in IPF.(13) The Song et al. trial also showed a statistical trend towards increased inflammation (i.e. diffuse lymphoplasmacytic infiltration) in CTD-UIP than in IPF.(13)
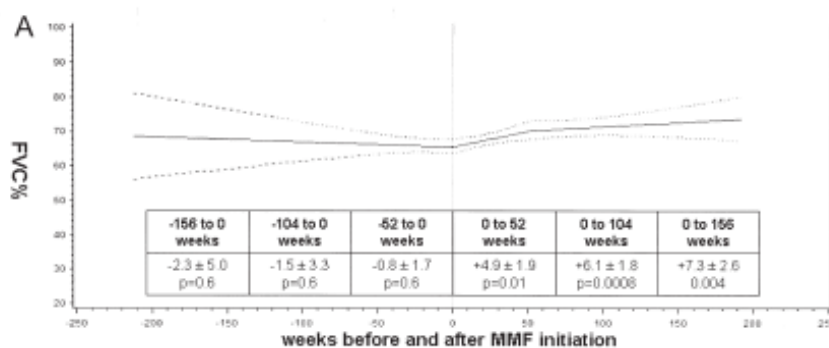
Preliminary Data

True preliminary data outside of some of the patient characteristics discussed above does not yet exist. However, two additional studies deserve mention. The first is a

study by Kim et al. from Korea, which is the largest cohort studied to date.(37) They used criteria similar to Corte, which are very similar to the IPAF criteria except that a morphologic domain was not included. All the patients defined as UCTD in this study thus had features that would fit in the clinical and serologic domains of the IPAF criteria. The study looked at 788 patients and found that 13.3% met the definition. The majority had UIP. Of the UIP patients though only 8% met the criteria as opposed to 23% of those with NSIP. Importantly, the outcome of the UCTD-UIP group was significantly better than IPF,
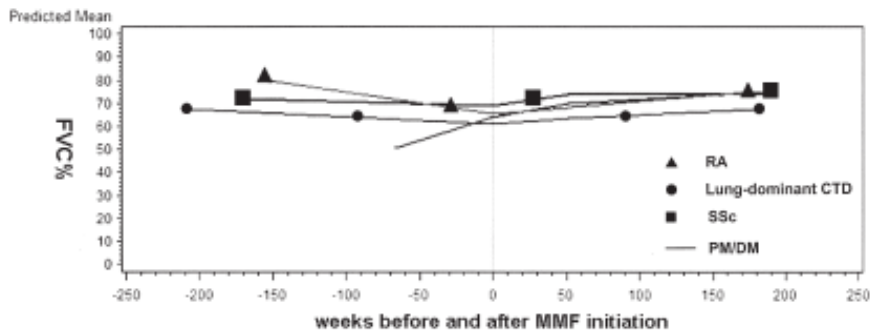

although not as good as UCTD NSIP. This is encouraging that the criteria are identifying a clinically distinct patient group and confirms some of the earlier work that the underlying pathologic pattern effects prognosis in IPAF patients.

The only data on therapy is in the retrospective cohort trial of mycophenolate mofetil use in CTD-ILD discussed above.(18) As shown in the figure below when all the CTD-ILD groups are combined mycophenolate use reversed the declining PFT trend as shown by mixed effects modeling.

Importantly, this study included patients with the LD-CTD designation and the PFT trend for that group followed a similar trajectory to the well-defined CTD patients as shown.

The study did not separate how many of the LD-CTD patients had UIP v. NSIP. However, the results are encouraging that an IPAF designation will have a meaningful therapeutic impact as well. Further study of larger populations with pre-defined subgroups according to the underlying pathologic pattern is still needed to have adequate preliminary data to justify multicenter randomized placebo controlled trials.

Conclusion

Studies show that approximately 15-25% of the patients that we would currently classify as idiopathic interstitial pneumonia have some clinical, serologic or morphologic features suggesting autoimmunity. Determining whether or not this group of patients behaves similar to patients with well-defined connective tissue disease or to patients with idiopathic interstitial pneumonia is crucial as the ramifications with regard to the diagnostic evaluation, prognosis and therapy are potentially large. The new consensus criteria to define this group as interstitial pneumonia with autoimmune features (IPAF) provides the necessary framework for future studies and is thus an important step forward. The available preliminary data suggests that patients meeting IPAF criteria have a better prognosis and possibly a different response to therapy than patients with IPF, the most common and severe form of idiopathic interstitial pneumonia. However, further study multicenter trials are needed.

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