Idiopathic Nonspecific Interstitial Pneumonia
Lung Manifestation of Undifferentiated Connective Tissue Disease?

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***Rationale*: The American Thoracic Society/European Respiratory Society International Consensus Classification panel identified the clinical entity idiopathic nonspecific interstitial pneumonia (NSIP) as a provisional diagnosis and recommended further study.**

***Objectives*: We hypothesized that idiopathic NSIP is an autoimmune disease and the lung manifestation of undifferentiated connective tissue disease (UCTD), a recently described, distinct entity.**

***Methods*: We studied 28 consecutive patients with idiopathic interstitial pneumonia (IIP) enrolled in the University of California, San Francisco Interstitial Lung Disease Center who met prespecified criteria for UCTD, as follows: at least one clinical manifestation of connective tissue disease, serologic evidence of systemic inflammation in the absence of clinical infection, and absence of sufficient American College of Rheumatology criteria for another connective tissue disease. Medical record reviews, evaluation of radiographs, and scoring of lung biopsies were performed. The control group consisted of all other patients (n = 47) with IIP who did not meet the UCTD criteria.**

***Measurements and Main Results*: The patients with UCTD were more likely to be women, younger, and nonsmokers than the IIP control subjects. Compared with the control group, patients with UCTD-ILD were significantly more likely to have ground-glass opacity on high-resolution computed tomography (HRCT) and NSIP pattern on biopsy, and less likely to have honeycombing on HRCT or usual interstitial pneumonia on biopsy. At our center, the majority of patients classified as idiopathic NSIP (88%) met the criteria for UCTD.**

***Conclusions*: Most patients diagnosed with idiopathic NSIP meet the case definition of UCTD. Furthermore, these results show that the clinical entity idiopathic NSIP is different from idiopathic pulmonary fibrosis and appears to be an autoimmune disease.**

Keywords: idiopathic interstitial pneumonia; systemic rheumatic disease; undifferentiated connective tissue; collagen vascular; autoimmune disease

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The clinical entity idiopathic nonspecific interstitial pneumonia is a provisional diagnosis and needs further study. Undifferentiated connective tissue disease is a recognized disease entity, but the pulmonary manifestations are not described. Their relationship is unknown.

What This Study Adds to the Field

Patients previously classified as having idiopathic nonspecific interstitial pneumonia have clinical, serologic, radiographic, and pathologic characteristics that are highly suggestive of autoimmune disease and meet criteria for undifferentiated connective tissue disease.

Before the last decade, a subset of the patients diagnosed as having idiopathic pulmonary fibrosis (IPF) had cellular biopsies (prominent lymphoplasmacytic inflammation), bronchoalveolar lavage lymphocytosis, a clinical response to steroids, and a better long-term prognosis (1–4). On review of the lung histopathology, most of these cases were reclassified as nonspecific interstitial pneumonia (NSIP) (i.e., their surgical lung biopsy showed a pattern, termed NSIP, distinct from usual interstitial pneumonia [UIP], the pattern characteristic of IPF) (5, 6). Consequently, the 2002 American Thoracic Society/European Respiratory Society (ATS/ERS) International Consensus Panel for Classification of Interstitial Lung Disease included idiopathic NSIP as a provisional clinical diagnosis and recommended further study and characterization of this condition (7).

The histopathologic pattern of NSIP has been found in a wide variety of clinical and radiologic contexts (8–10). Recently, NSIP has been identified as the most common histopathologic pattern found in patients with connective tissue disease (CTD) who meet established American College of Rheumatology (ACR) criteria (11–13).

Rheumatologic studies have estimated that up to 25% of patients with features of a systemic autoimmune disease do not fulfill ACR classification criteria for CTD (14–18). These patients are considered to have diffuse or undifferentiated CTD (UCTD). The majority of such cases (65–94%) after years of follow-up do not develop into a "differentiated" CTD (e.g., rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, mixed CTD) (14–19). Consequently, it has been proposed that UCTD represents a distinct clinical entity with the following criteria: signs and symptoms suggestive of a CTD, positive serologic results, and disease duration of at least 1 year (19–21). The most common clinical manifestations of UCTD include the following: Raynaud's phenomenon, arthritis/arthralgias, pleuritis/pericarditis, sicca symptoms, cutaneous involvement (photosensitivity, rash), esophageal involvement, fever, and myositis (14). The specific pulmonary manifestations of UCTD have not been studied.

We hypothesized that the clinical entity "idiopathic NSIP" is an autoimmune disease and, furthermore, is the lung manifestation of UCTD. Applying prespecified diagnostic criteria for UCTD to a cohort of patients with idiopathic interstitial pneumonia (IIP), we studied these patients' clinical manifestations, radiographic findings, and lung histopathologic patterns. Next, we compared the patients with UCTD with all other patients with IIP enrolled at the University of California, San Francisco (UCSF), over the same period. Last, we determined what proportion of patients with IIP and a lung biopsy showing NSIP pattern met the case definition for UCTD. Some of the results

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of this study were presented in abstract form at the ATS International Conference in May 2007 (22).

METHODS

Study Subjects and Diagnostic Criteria

We reviewed the medical records of patients consecutively enrolled in the UCSF Interstitial Lung Disease longitudinal database with a diagnosis of IIP from January 1, 2004, to November 1, 2006. Enrollment included completion of a written survey and permission to review all medical records. The UCSF Committee on Human Research approved the study, and subjects provided informed consent.

Patients were considered to have UCTD if review of their medical record identified signs or symptoms and laboratory findings that met the prespecified criteria for UCTD as defined in Table 1. Patients with a defined CTD according to current ACR criteria, or a known cause of interstitial lung disease (ILD) (e.g., hypersensitivity pneumonitis, drug-induced lung disease) were excluded. Using this approach, 28 patients were identified who met the criteria for UCTD. For the control group, we reviewed the medical records of all the other patients with IIP (n = 47) from our original query and who did not meet the case definition for UCTD.

Clinical and Radiographic Characteristics

Patients entered into the database had the following clinical characteristics documented at the time of the first visit: age, ethnicity, sex, date of first symptom onset (cough, dyspnea, or wheeze), symptoms or signs of CTD (Table 1), smoking status, physical exam findings, pulmonary function tests, and serologic tests (the battery of individual tests were determined by individual clinician judgment). Serologic studies were performed in a variety of laboratories, including referring clinics/hospitals and at the study hospital, using standard techniques (23, 24). All laboratory tests were ordered as part of clinical evaluation and not performed for the purposes of this study.

High-resolution computed tomography (HRCT) scans of the chest were performed on all patients at the time of initial evaluation. For this study, the films were reviewed in a blinded fashion by chest radiologists experienced in the interpretation of diffuse lung disease. The specific findings on HRCT were documented for the index scan (first documenting presence of ILD).

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

* Criteria are derived from References 18, 20, and 21.

Pathologic Analysis

All lung biopsy specimens were reviewed by a lung pathologist at UCSF with experience and advanced training in the evaluation of diffuse lung disease, and were classified using the histopathologic patterns described in the ATS/ERS International Consensus Classification of the IIPs (7). Specific features on histopathology were prospectively documented and a major histopathologic pattern was assigned as part of clinical care and without knowledge of this particular study.

Determination of Overlap between UCTD and IIP with Biopsy Pattern of NSIP

After the above analyses were performed, the entire UCSF ILD longitudinal database was reviewed to identify all patients classified as IIP with a surgical biopsy documenting an NSIP pattern. This list was then cross-referenced with all patients fulfilling criteria for UCTD. The proportion of patients with UCTD among those with IIP and a biopsy showing NSIP was determined.

Statistical Analysis

Continuous data are expressed as means or medians with observed range. Categorical data are expressed as percentages. Comparisons between groups were made using the t test, χ^2 test, or Fisher exact test as appropriate. All p values corresponded to two-sided tests and statistical significance was defined as a p value of less than 0.05. All analyses were performed with STATA statistical software (version 9.2; Stata Corp., College Station, TX).

RESULTS

Study Population

Two hundred and eighty patients were enrolled in the UCSF database during the study period (78 with IIP, 53 with defined CTDs, 44 with sarcoidosis, 40 with hypersensitivity pneumonitis, 28 with drug-induced ILD, 6 with asbestosis, 31 with miscellaneous other diagnoses or diagnostic uncertainty but not believed to be idiopathic). Among the established CTD-associated ILDs (cases that were excluded from this study), 33 had scleroderma, 8 had rheumatoid arthritis, 7 had dermatomyositis/polymyositis, 3 had primary Sjögren's disease, 1 had systemic lupus erythematosus, and 1 had mixed connective tissue disease.

Seventy-five subjects with IIP had adequate data and 28 of these met criteria for UCTD (37%). This represents approximately 10% (period prevalence) of all patents enrolled in the UCSF ILD clinic during the study period. Forty-seven control patients with IIP who did not meet criteria for UCTD constituted the control cohort (Figure 1A). Of these, 41 were diagnosed as IPF, 2 as having idiopathic NSIP, 1 with desquamative interstitial pneumonia, and 3 did not have a biopsy and a final clinical diagnosis was inconclusive (the differential diagnosis was fibrotic NSIP vs. IPF).

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the 28 patients with UCTD and the 47 control patients with IIP studied are shown in Table 2. Sixty-eight percent of the patients with UCTD were women compared with 23% of the IIP control subjects ($p < 0.0001$). The mean age of disease onset (defined by first attributable lung symptom) was 50 years for the patients with UCTD and 65 years for the control subjects with IIP ($p < 0.0001$). Forty-three percent of patients with UCTD and 75% of the control IIP patients were ever-smokers ($p = 0.006$). The most common ethnicity in both groups of patients was white.

As expected based on the case criteria, systemic but not respiratory symptoms could differentiate between the patients with UCTD and the other IIP control subjects. All patients presented with dyspnea. Dry cough was somewhat less common in the UCTD group (82 vs. 98%, $p = 0.015$). In the UCTD group,

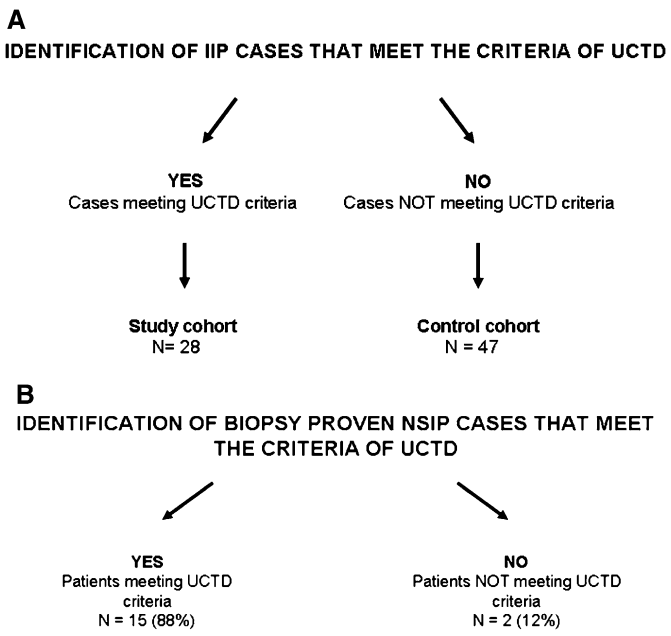

Figure 1. (*A*) Flow diagram for determining undifferentiated connective tissue disease (UCTD) cases and control subjects. All cases enrolled from January 1, 2004, to November 1, 2006, with diagnosis of idiopathic interstitial pneumonia (IIP; n = 75) were reviewed to identify those that met the criteria for UCTD (*see* Table 1). (*B*) Flow diagram showing the proportion of patients with nonspecific interstitial pneumonia (NSIP) on biopsy that met the criteria for UCTD. All cases enrolled from January 1, 2004, to November 1, 2006, with a diagnosis of IIP and with a lung biopsy showing an NSIP pattern were examined (n = 17).

the most common systemic symptoms were arthralgias/joint swelling (64%) and Raynaud's phenomenon (61%). Other common findings included the following: esophageal symptoms such as gastroesophageal reflux (65%) and dysphagia (36%), dry mouth or eyes (29%), recurrent unexplained fever (25%), rash (25%), and morning stiffness (18%). Twenty-four (86%) of the patients with UCTD had at least two symptoms, whereas 19 (67%) had at least three systemic symptoms. Twelve (43%) of the patients had both arthralgias and Raynaud's phenomenon. In the control group, these symptoms were much less common. Clubbing was seen in 7% of those with UCTD and in 26% of control subjects ($p = 0.048$), whereas inspiratory crackles were common in both groups (89 and 96%, respectively).

Laboratory and Physiologic Findings

Laboratory data are displayed in Table 3. A positive antinuclear antibody was the most common serologic abnormality in patients with UCTD (64%), with a median titer of 1:320. In addition, these patients frequently had a sedimentation rate more than two times the upper limit of normal (67%). A positive antinuclear antibody was decidedly uncommon in the control group (6%), and when present, was of low titer (1:40 and 1:80).

The pulmonary function abnormalities were similar between the two groups and demonstrated restrictive defects with diffusion impairments.

Chest Imaging Findings

Results of the comparison between the two groups for characteristic features on HRCT are shown in Table 4. The finding of ground-glass opacity extending beyond areas of adjacent reticulation was highly associated with the UCTD patient group (odds ratio [OR], 49; $p < 0.0001$). In addition, the finding of consolidation was also associated with having UCTD (OR, 10; $p = 0.025$). In contrast, the finding of honeycombing (OR for UCTD, 0.06; $p < 0.0001$) and traction bronchiectasis (OR for UCTD, 0.23; $p = 0.006$) was much more characteristic of the other IIPs than with UCTD. Mosaic perfusion was more common in the UCTD group but the difference was not statistically significant ($p = 0.36$). Reticulation was a common feature in both groups.

Histopathologic Findings

Table 5 shows the histopathologic patterns for all study patients who underwent surgical lung biopsy (n = 40; 18 [64%] met criteria for UCTD, and 22 [47%] had other IIPs) and provides a comparison between the UCTD and control groups. Overall, UIP was the most common pattern (50%) followed by NSIP (43%). There was one case each of organizing pneumonia, desquamative interstitial pneumonia, and nonclassifiable fibrosis.

Among the 28 cases who met the UCTD criteria, 18 underwent surgical lung biopsy, the NSIP pattern was present in 15 patients (OR, 50; $p < 0.0001$); in the remaining three cases, there was one case each of organizing pneumonia, UIP, and nonclassifiable fibrosis. Among the 22 cases with IIP who underwent surgical lung biopsy and who did not meet the UCTD case definition, two patients had an NSIP pattern found on lung biopsy. Therefore, among all patients enrolled in the UCSF database with IIP and an NSIP pattern on surgical lung biopsy during this study period (n = 17), 15 (88%) met our case definition for UCTD (Figure 1B). It is noteworthy that the two patients who did not meet the UCTD case definition met the systemic symptom criteria and had ground-glass opacity on HRCT but did not meet serologic criteria; however, complete serologic panels were not performed. The UIP pattern was strongly associated with the other IIP group (OR for control subjects, 111; OR for UCTD, 0.009; $p < 0.0001$).

DISCUSSION

Even in the absence of a defined CTD, 10 to 20% of patients with IIP have systemic symptoms (fever, arthralgias, Raynaud's phenomenon) and serologic abnormalities (elevated erythrocyte sedimentation rate, antinuclear antibodies, or rheumatoid factor) suggestive of an autoimmune process (25–27). Following the 2002 ATS/ERS international consensus classification of the IIPs, it has been noted that most patients with these findings are classified among the patients with idiopathic NSIP (3, 28). In addition, it is now recognized that the vast majority of ILD associated with defined CTD is characterized by the histopathologic pattern of NSIP (11–13) and a predominance of ground-glass opacities on HRCT (13, 29, 30), especially in systemic sclerosis, Sjögren's syndrome, and dermatomyositis/polymyositis. A recent ATS working group described idiopathic NSIP as a distinct clinical entity that occurs mostly in middle-aged women who are never-smokers and who often have positive serologic tests for collagen vascular disease (31). Fujita and coworkers recently reported in a case series that the clinical and pathologic features of patients with idiopathic NSIP and those with CTD-associated NSIP were qualitatively similar (32). Given the above, we hypothesized that the clinical entity "idiopathic NSIP" is an autoimmune disease and the lung manifestation of UCTD, an increasingly recognized and distinct CTD. Our results provide strong evidence to support this hypothesis. In addition, the high prevalence ($\sim 10\%$) of these patients in a tertiary referral center population demonstrates the importance of this disorder.

Several characteristics of the current study enhance the validity of the results: the systematic prospective assessment for symptoms of CTD, detailed information on clinical and

TABLE 2. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WITH UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE COMPARED WITH PATIENTS WITH IDIOPATHIC INTERSTITIAL PNEUMONIA

Characteristics	Patients with UCTD* (*n = 28*)	Patients with other IIP† (*n = 47*)	p Value‡
Age at first lung symptom, yr, mean (range)	50 (31–68)	65 (41–86)	< 0.0001
Age at first enrollment, yr, mean (range)	54 (33–69)	69 (46–90)	< 0.0001
Sex, n (%)			
Men	9 (32)	36 (77)	< 0.0001
Women	19 (68)	11 (23)	
Smoking status, n (%)			
Ever	12 (43)	35 (75)	0.006
Never	16 (57)	12 (25)	
Former	12 (43)	32 (68)	
Current	0	3 (11)	
Ethnic background, n (%)			
White	19 (68)	39 (83)	0.077
Black	1 (4)	4 (9)	
Hispanic	4 (14)	4 (9)	
Asian	3 (11)	0 (0)	
Other	1 (4)	0 (0)	
Symptoms and signs at presentation, n (%)			
Lung related			
Dyspnea	28 (100)	47 (100)	
Cough	23 (82)	46 (98)	0.015
Wheeze	2 (7)	1 (2)	0.284
Systemic			
Arthralgias/joint swelling	18 (64)	6 (13)	< 0.001
GERD	18 (65)	16 (34)	0.011
Raynaud's phenomenon	17 (61)	0 (0)	< 0.001
Dysphagia	10 (36)	2 (4)	< 0.001
Sicca symptoms	8 (29)	6 (13)	0.089
Recurrent fever	7 (25)	2 (4)	0.007
Skin changes (rash)	7 (25)	1 (2)	0.002
Morning stiffness	5 (18)	0 (0)	0.003
Unintentional weight loss	3 (11)	5 (11)	0.992
Proximal muscle weakness	3 (11)	0 (0)	0.022
Oral ulcerations	1 (4)	0 (0)	0.192
Photosensitivity	0	0	
Alopecia (nonandrogenic)	0	0	
Bibasilar inspiratory crackles	25 (89)	45 (96)	0.278
Clubbing	2 (7)	12 (26)	0.048

Definitions of abbreviations: GERD = gastroesophageal reflux disease; IIP = idiopathic interstitial pneumonia; UCTD = undifferentiated connective tissue disease.

* Includes patients with UCTD (*see* Table 1 for definitions).

† IIP control subjects (clinical diagnoses include 24 subjects with idiopathic pulmonary fibrosis, 3 with idiopathic nonspecific interstitial pneumonia, and 1 with desquamative interstitial pneumonia).

‡ χ^2 or Fisher exact test, where appropriate.

radiographic characteristics, and documentation of specific histopathologic findings. This study is the first to apply specific criteria for the diagnosis of UCTD to characterize patients with associated ILD. We show that patients with UCTD and ILD bear striking similarities to the more established CTDs in terms of clinical characteristics (female, younger, nonsmoker predilection, high titer-positive antinuclear antibodies (ANA), absence of clubbing), radiographic features (presence of significant ground-glass opacity and absence of honeycombing), and histopathologic patterns (NSIP predominant). We believe this study provides important insight into the underlying pathogenesis of these patients—that of autoimmunity.

Autoimmune disease predominantly affecting a single-organ system is well described (33, 34). The establishment of these diseases as autoimmune in nature has largely been based on clinical and laboratory evidence of autoimmunity, and histologic findings of a lymphocytic infiltrate in the affected organ (33, 34). In autoimmune pancreatitis, internationally recognized criteria are based on a combination of the findings of abdominal imaging, laboratory testing (positive autoantibodies), and histology (lymphoplasmacytic infiltrate) (35). Other investigators have suggested the inclusion of a clinical response to steroids in the criteria (36). In autoimmune hepatitis, the diagnosis is based on characteristic clinical features (e.g., female predilection, systemic symptoms such as arthralgias), circulating autoantibodies (e.g., ANA titer greater than 1:80), abnormal levels of serum globulins, and a compatible histologic picture (chronic hepatitis with a plasma cell infiltrate) (34). Although the causes of autoimmune hepatitis and pancreatitis are unknown, aberrant autoreactivity is believed to have a role in its pathogenesis. Based on similar clinical, laboratory, and histopathologic criteria, we believe our findings suggest that idiopathic NSIP represents a form of autoimmune pneumonitis.

In the 2002 ATS/ERS international consensus statement on the classification of IIP, it was stated that, "the concept of an idiopathic form of NSIP presents a problem for the clinician because there is no recognized and distinctive clinical description for patients presenting with this histologic pattern on lung biopsy" (7). Our study suggests that the application of diagnostic criteria for UCTD may be able to distinguish these patients based on a thorough systematic review of symptoms or signs of CTD and serologic studies before obtaining surgical lung biopsy.

TABLE 3. LABORATORY AND PULMONARY FUNCTION DATA OF PATIENTS WITH UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE COMPARED WITH PATIENTS WITH IDIOPATHIC INTERSTITIAL PNEUMONIA

	UCTD*		Other IIP Patients†	
Characteristic	No. of Patients Examined	Median or Number (%)	No. of Patients Examined	Median or Number (%)
Laboratory				
Anti–nuclear antibody, positive	28	18 (64)	33	2 (6)
Anti–nuclear antibody titer, median (range)	18	320 (40–1,280)	2	60 (40–80)
Rheumatoid factor, positive	26	5 (19)	29	2 (7)
Anti–SSA‡ antibody, positive	17	2 (12)	6	0 (0)
Anti–SSB§ antibody, positive	17	0	6	0 (0)
Anti–SCL‖ 70 antibody, positive	19	1 (5)	9	0 (0)
CCP¶ positive	3	0	2	0 (0)
Anti-RNP, positive	9	0	3	0 (0)
Sedimentation rate (> 2× normal)	12	8 (67)	4	0 (0)
Anti–Jo1** antibody, positive	9	2 (22)	1	0 (0)
Other serology,†† positive	15	9 (60)	9	0 (0)
Pulmonary function tests at presentation				
FVC, % predicted (range)	28	62.5 (38–104)	46	69 (36–119)
D_{LCO}, % predicted (range)	27	47 (16–64)	44	47 (14–73)
TLC, % predicted (range)	24	66 (47–87)	39	64 (45–101)

Definition of abbreviations: anti-RNP = antiribonucleoprotein; IIP = idiopathic interstitial pneumonia; UCTD = undifferentiated connective tissue disease.

* Includes patients with UCTD (*see* Table 1 for definition).

† IIP control subjects (clinical diagnoses include 41 with idiopathic pulmonary fibrosis, 2 with idiopathic nonspecific interstitial pneumonia, 1 with desquamative interstitial pneumonia, and 3 with inconclusive nonspecific interstitial pneumonia vs. idiopathic pulmonary fibrosis).

‡ Also known as anti–Ro antibody.

§ Also known as anti–La antibody.

‖ Also known as anti–topoisomerase I antibody.

¶ Also known as anti–cyclic citrullinated peptide antibody.

** Also known as anti–histidyl-tRNA synthetase.

†† Other labs included C-reactive protein, creatine kinase, aldolase.

It has been known for some time that the pulmonary manifestations of CTD occasionally precede the more typical systemic manifestations by months or years (especially in rheumatoid arthritis, systemic lupus erythematosus, and polymyositis/dermatomyositis) (37). Consequently, we expect that some of the patients included in our UCTD cohort will go on to develop sufficient criteria to be classified as another disease entity. However, if patients with ILD behave similarly to those with UCTD in general, this is likely to be a minority of patients (e.g., 25%) (14–19). Furthermore, among those patients with UCTD that does evolve into another disorder, the majority do so within the first year of follow-up (19). It should be noted that our UCTD patients with ILD had mean disease duration (first pulmonary symptom onset until presentation) of approximately 3.5 years at the time of enrollment.

We have demonstrated that the most common clinical manifestations in patients with UCTD and ILD are diffuse arthralgias, Raynaud's phenomenon, and esophageal symptoms, whereas oral ulcerations, renal and neurologic disease (data not shown), alopecia, clubbing, and muscle weakness are uncommon. This relative frequency of findings are similar to what has been observed in other non-ILD UCTD cohorts (19). These findings, if replicated, may inform subsequent development of more specific classification criteria for this form of CTD.

TABLE 4. HIGH-RESOLUTION COMPUTED TOMOGRAPHY FINDINGS IN PATIENTS WITH UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE COMPARED WITH PATIENTS WITH IDIOPATHIC INTERSTITIAL PNEUMONIA

Characteristic	UCTD* n 28 (%)	Other IIP† n = 47 (%)	OR (*95% CI*)	p Value‡
Ground-glass opacity§	21 (75)	4 (9)	49 (10–261)	< 0.0001
Consolidation	5 (21)	1 (2)	10 (1.0–483)	0.025
Reticulation	24 (86)	45 (96)	0.20 (0.02–1.40)	0.100
Traction bronchiectasis	18 (64)	37 (79)	0.23 (0.07–0.73)	0.006
Honeycombing	3 (11)	37 (79)	0.06 (0.01–0.22)	< 0.0001
Mosaic perfusion	4 (14)	2 (4)	2.7 (0.29–34)	0.356

Definition of abbreviations: CI = confidence interval; IIP = idiopathic interstitial pneumonia; OR = odds ratio; UCTD = undifferentiated connective tissue disease.

* Includes patients with UCTD (*see* Table 1 for definition).

† IIP control subjects (clinical diagnoses include 41 with idiopathic pulmonary fibrosis, 2 with idiopathic nonspecific interstitial pneumonia, 1 with desquamative interstitial pneumonia, and 3 with inconclusive nonspecific interstitial pneumonia vs. idiopathic pulmonary fibrosis).

‡ χ^2 or Fisher exact test, where appropriate.

§ Defined as a significant amount of ground-glass opacification beyond that associated with reticulation.

TABLE 5. HISTOPATHOLOGIC FINDINGS IN PATIENTS WITH UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE COMPARED WITH PATIENTS WITH IDIOPATHIC INTERSTITIAL PNEUMONIA

Histopathologic Pattern	All Patients n = 40 (%)	UCTD* n = 18 (%)	Other IIP† n = 22 (%)	OR (95% CI)	p Value‡
Nonspecific interstitial pneumonia pattern	17 (42.5)	15 (83)	2 (9)	50 (6–566)	< 0.0001
Usual interstitial pneumonia	20 (50)	1 (6)	19 (86)	0.009 (0.0002–0.114)	< 0.0001
Organizing pneumonia	1 (2.5)	1 (6)	0 (0)	NS	0.450
Desquamative interstitial pneumonia	1 (2.5)	0 (0)	1 (5)	NS	1
Nonclassifiable fibrosis	1 (2.5)	1 (6)	0 (0)	NS	1

Definition of abbreviations: CI = confidence interval; IIP = idiopathic interstitial pneumonia; NS = not significant; OR = odds ratio; UCTD = undifferentiated connective tissue disease.

* Includes patients with UCTD (*see* Table 1 for definition).

† IIP control subjects (clinical diagnoses include 41 with idiopathic pulmonary fibrosis, 2 with idiopathic nonspecific interstitial pneumonia, 1 with desquamative interstitial pneumonia, and 3 with inconclusive nonspecific interstitial pneumonia vs. idiopathic pulmonary fibrosis).

‡ χ^2 or Fisher exact test, where appropriate.

There are a number of limitations of this study. First, in keeping with the most recently published literature on the topic (19, 20), we chose to only require one connective tissue symptom for the diagnosis of UCTD. This approach may sacrifice some specificity and potentially lead to misclassification. If present, the direction of misclassification would be expected to bias our results toward the null hypothesis, because patients without true UCTD would have been misclassified as cases instead of control subjects. Importantly, the overwhelming majority of patients with UCTD-ILD had more than one symptom (86%) and most had at least three symptoms (67%). Second, although the study demonstrated several highly statistically significant associations, the sample size limited our power to examine some of the less dramatic but potentially insightful associations (e.g., mosaic perfusion on HRCT or germinal centers on histopathology). Third, the retrospective design limited our ability to acquire a complete serologic panel on all patients. Consequently, in our case definition, we had to include a requirement for at least one of several potential autoantibodies/inflammatory markers. In addition, we included sedimentation rate and C-reactive protein (in absence of infection) in our criteria to be as inclusive as possible because of the absence of prior description of UCTD in the setting of ILD. Although these tests are relatively nonspecific, they are frequently used to monitor disease activity of rheumatic diseases (38). We would note again, however, that if misclassification occurred, it would have been expected to bias our results toward the null hypothesis. In future prospective studies, it will be important to perform comprehensive laboratory and serologic panels on all patients to more precisely elucidate these patterns.

In summary, we have demonstrated that most patients previously classified as having idiopathic NSIP have clinical, serologic, radiographic, and pathologic characteristics that are suggestive of autoimmune disease and meet criteria for UCTD. Future studies should confirm these findings in other cohorts of patients with ILD, define the natural history of UCTD-ILD, and identify appropriate targets for well-designed controlled studies of therapeutic interventions.

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