Chapter 6

Interstitial lung disease with autoimmune features

B.W. Kinder

Summary

The aetiology and classification of interstitial lung diseases have been a challenge for many years. Recent data suggests that a particular subset of patients previously classified as having an idiopathic interstitial pneumonia have extrathoracic symptoms and signs, laboratory features, and histopathological findings that are suggestive of an autoimmune aetiology of their interstitial lung diseases when carefully assessed. Although data are limited, it appears that patients with interstitial lung diseases and autoimmune features may have a better prognosis and be more responsive to treatment than patients with idiopathic pulmonary fibrosis. Barriers to appropriate case recognition and classification need to be addressed at local, national, and international levels.

Keywords: **Autoimmune, connective tissue disease, idiopathic interstitial pneumonia, nonspecific interstitial pneumonia, undifferentiated connective tissue disease**

Correspondence: B.W. Kinder, 2055 Hospital Drive, Suite 200, Batavia, OH 45103, USA.
Email: bwkinder2011@gmail.com

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The aetiology and classification of interstitial lung diseases (ILD) have been a constant challenge for scientists and clinicians interested in respiratory diseases for many years. ILD can occur in patients with an identifiable underlying cause of lung injury (*i.e.* environmental exposure or a systemic disease such as rheumatoid arthritis (RA)) or in isolation where the disease is classified as idiopathic or cryptogenic. Pathologists have led many of the advancements in the classification of the idiopathic interstitial pneumonias (IIP) in the past few decades [1, 2]. Histopathological evaluation has shown the traditional clinical diagnosis of IIP to be more heterogeneous than once thought [3]. The sub-classification of IIPs, based on clinico-radiologic-pathological criteria, has important therapeutic and prognostic implications. These prognostic and treatment efficacy differences have led to an increased interest and, subsequently, understanding of the IIPs. Recent data suggests that a particular subset of patients previously classified as having an IIP have extrathoracic symptoms and signs, laboratory features, and histopathological findings that are suggestive of an autoimmune aetiology of their ILD when carefully assessed [4].

Nonspecific interstitial pneumonitis

Prior to the past decade, a subset of the patients diagnosed as having idiopathic pulmonary fibrosis (IPF) had cellular infiltration on lung biopsy (prominent lymphoplasmacytic inflammation), bronchoalveolar lavage lymphocytosis, a clinical response to steroids and a better long-term prognosis [5–8]. On retrospective evaluation 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 [9, 10]. Consequently, in 2002, a joint American Thoracic Society/European Respiratory Society International Consensus Panel for the classification of ILD included idiopathic NSIP as a provisional clinical diagnosis and recommended further investigation and characterisation of this condition [11]. The NSIP pattern is also found on surgical lung biopsies from non-idiopathic forms of interstitial lung disease, such as well-defined connective tissue disease (CTD; as discussed below), hypersensitivity pneumonitis and drug induced pneumonitis. Thus, the clinical context and features are critical in evaluating a patient with an NSIP pattern on surgical lung biopsy. A thorough history, including a detailed review of occupational endeavours, domiciliary environment and medication use (both current and prior), and a systematic review of symptoms for evidence of CTD are critical for appropriate diagnosis, classification and treatment of any patient with an NSIP pattern of lung injury.

ILD in systemic rheumatic (or autoimmune) diseases

CTDs are associated with a variety of diffuse parenchymal lung diseases (DPLD). The most common manifestation across specific disease entities is ILD. Although the association between CTD and ILD has been known clinically for decades, there are few high-quality well-controlled studies of these patients. In the past, these disorders were evaluated and managed similarly to the IIPs, such as IPF.

Characteristics of individual CTDs

Scleroderma or systemic sclerosis

Lung involvement is common in this disease with prevalence estimates of up to 80% [12]. Diffuse ILD is the most common pulmonary manifestation followed by pulmonary hypertension. Using pulmonary function test data, clinically significant pulmonary involvement is detectable in 25% of the patients with systemic sclerosis within 3 yrs of initial diagnosis [13–15]. In general, the degree of pulmonary involvement by scleroderma is not correlated with the extent of extrapulmonary involvement [16]. Early pulmonary involvement is often asymptomatic. The impact of pulmonary involvement is demonstrated by the fact that it is now the leading cause of death in this patient population [12].

Rheumatoid arthritis

There are a wide variety of lung manifestations associated with RA, including ILD, airways disease (bronchiectasis, bronchiolitis and cricoarytenoid arthritis), pleural disease and pulmonary vascular disease. The incidence of ILD in RA depends on the methods of its detection and the population selected for study, but it appears that while up to 58% may have some evidence of disease, only 14% have clinically significant disease [17]. Recent data suggests that ILD is becoming a major cause of RA-related morbidity and mortality. A study by Olson *et al.* [18], using national health record data from the USA, showed that clinically significant RA-ILD occurs in a minimum of 10% of the RA population, and is associated with shortened survival and more severe underlying disease. While overall mortality rates in RA have fallen, those associated with RA-ILD have increased significantly in older age groups.

Polymyositis/dermatomyositis

It is unclear what the true prevalence of lung involvement in this disorder is, but in a study of 81 patients with polymyositis/dermatomyositis (PM/DM), 61% of patients had evidence of lung involvement, approximately two-thirds of whom had ILD [19]. There are no high-quality data to document how many of these cases are ''clinically significant''. However, in my clinical experience most cases that come to clinical attention result in symptomatic impairment. Other lung manifestations include aspiration pneumonitis and, less commonly, pulmonary hypertension or pleural disease. PM/DM may precede (months to years) the muscle complaints or be superimposed on established muscle disease. Occasionally, asymptomatic patients demonstrate significant physiologic and roentgenographic abnormalities consistent with ILD. There appears to be no correlation between the severity or duration of the muscular disease and the ILD. In a retrospective study of 156 patients in France, 25% of patients with ILD had progressive disease and 20% had improvement/stabilisation, suggesting a heterogeneous disease course [20].

Systemic lupus erythematosis

Any portion of the respiratory tract, as well as the pleura, may be involved in patients with systemic lupus erythematosis (SLE), with the most common manifestations including pleural disease, pulmonary vascular disease and infectious pneumonia. ILD in SLE primarily consists of the three following manifestations: acute lupus pneumonitis (acute interstitial pneumonia or diffuse alveolar damage); chronic interstitial pneumonia (NSIP); and lymphocytic interstitial pneumonia (LIP). Chronic ILD is an uncommon manifestation of SLE. In my experience, interstitial lung changes can be seen in lupus patients that are otherwise asymptomatic and may not be clinically significant. Most investigators believe that there is an evolution from acute to chronic ILD based on examples of persistent disease after an acute onset, mixed acute and chronic roentgenographic patterns, histopathologic evidence of transition from an inflammatory cellular infiltrate to a fibrotic lesion, and the somewhat younger ages of the acute (mean age 38 yrs) as opposed to the chronic (mean age 46 yrs) cases [21].

Sjögren's syndrome

Pulmonary manifestations occur frequently in Sjögren's syndrome [22, 23]. However, because of the common association with other CTD, it has been difficult to determine if the pulmonary manifestation is a manifestation of Sjögren's syndrome and not of the coexistent CTD. In a recent study of 33 patients, ILD was the most common manifestation (61%), followed by bronchiolitis (12%) and lymphoma (12%) [24]. The pathological pattern most often seen in association with Sjögren's syndrome is NSIP or LIP.

Mixed CTD

These patients were originally defined as having a CTD characterised by the presence of high titres of a distinctive autoantibody called anti-U1-RNP (previously termed anti-ENA) [25]. The basic idea of the mixed CTD concept is that of an overlap syndrome which embraces features of SLE, scleroderma and PM. Mixed CTD is a distinct entity that should be distinguished from undifferentiated CTD (see below) in that its criteria includes the distinctive autoantibody, anti-U1-RNP, and patients often fulfil criteria for other CTDs. Pleuro-pulmonary disease commonly complicates the course of mixed CTD, with up to 82% of patients demonstrating evidence of pulmonary dysfunction [26]. The most common manifestations include ILD, aspiration pneumonitis, pulmonary vascular disease and pleurisy with or without an effusion. It is generally believed that ILD is common in patients with mixed CTD but this belief may be subclinical.

Histopathological patterns

Several patterns of lung injury have been reported in computed tomography (CT)-associated DPLD including: cellular interstitial pneumonia or NSIP, UIP-like pattern, bronchiolitis obliterans-organising pneumonia, LIP, diffuse alveolar damage (DAD), diffuse alveolar haemorrhage, bronchiolitis obliterans, and lipoid pneumonia. In CT-associated ILD, it is common to have a mixed pattern of pathologic injury with features including: temporally homogeneous fibrosis, airway-centred germinal centres and lymphoplasmacytic cellular infiltrate, follicular bronchiolitis, and areas of organising pneumonia. Several of the specific diseases have also been shown to have a diffuse alveolar damage pattern presenting with acute and/or fulminant disease. Overall, the most common pattern is that of NSIP. The relative prevalence of histopathological patterns has been studied in several of the particular diseases as follows.

In a study of 80 patients with systemic sclerosis-associated ILD, the NSIP pattern was seen in 77.5% of patients compared to 7.5% each with a UIP-like pattern, end-stage lung disease, and others [27].

In a study of 18 patients with RA-associated ILD, 10 patients were reported to have a UIP-like pattern, six an NSIP pattern, and two patients had inflammatory airway disease and organising pneumonia pattern [28].

In a study of 70 patients with ILD and either DM or PM, in which 22 had open lung biopsies, NSIP was seen in 18 (81.8%) out of 22 patients, organising DAD in two, bronchiolitis obliterans-organising pneumonia in one and UIP-like pattern in one patient [29].

A common feature is lymphocytic infiltration in several patterns: follicular bronchiolitis, LIP, nodular lymphoid hyperplasia, and lymphoma. It is unclear whether there is an evolution from one pattern to another. In a study of 33 patients, NSIP was seen in the majority (61%) of patients [24].

Undifferentiated CTD

Rheumatological studies have estimated that up to one-quarter of patients with features of a systemic autoimmune disease do not fulfil the American College of Rheumatology (ACR) classification criteria for CTD [30–34]. These patients are considered to have diffuse or undifferentiated CTD. After years of follow-up, the majority of such cases (65–94%) do not develop into a ''differentiated'' CTD (such as RA, SLE, systemic sclerosis, mixed CTD, *etc.*) [30–35]. Consequently, it has been proposed that undifferentiated CTD represents a distinct clinical entity with the following criteria: signs and symptoms suggestive of a CTD, positive serological results, and disease duration of at least 1 yr [35–37]. The most common clinical manifestations of undifferentiated CTD in rheumatological populations include: Raynaud's phenomenon, arthritis/arthralgias, pleuritis/pericarditis, sicca symptoms, cutaneous involvement (photosensitivity, rash), oesophageal involvement, fever, and myositis [30]. The specific pulmonary manifestations of undifferentiated CTD in a respiratory disease population have only recently been investigated [4]. In this study it was shown that several patients presenting with ''idiopathic'' NSIP often have features suggestive of CTD and meet criteria for undifferentiated CTD (table 1).

It has been known for some time that the pulmonary manifestations of CTD occasionally precede the more typical systemic manifestations by months or years and are considered *forme frustes* of CTD (especially in RA, SLE and PM/DM) [38]. Consequently, one could expect that some of the patients initially diagnosed as undifferentiated CTD-ILD will go on to develop sufficient criteria to be classified as another disease entity. However, in general, if patients with ILD behave similarly to those with undifferentiated CTD, this is likely to be a minority of patients (*e.g.* 25%) [30–35]. Furthermore, among those patients with undifferentiated CTD who do evolve into another disorder, the majority do so within the first year of follow-up [35]. A recent study suggested that vitamin D deficiency in undifferentiated CTD patients may play a role in the subsequent progression into well-defined CTDs [39]. To date, there are no prospective data published regarding the rate of evolution to another CTD among patients with undifferentiated CTD-ILD.

Table 1. Diagnostic criteria for patients with undifferentiated connective tissue disease

Symptoms associated with connective tissue disease
At least one of the following symptoms:
Raynaud's phenomenon
Arthralgias/multiple joint swelling
Photosensitivity
Unintentional weight loss
Morning stiffness
Dry mouth or dry eyes (sicca features)
Dysphagia
Recurrent unexplained fever
Gastro-oesophageal reflux
Skin changes (rash)
Oral ulceration
Nonandrogenic alopecia
Proximal muscle weakness
Evidence of systemic inflammation in the absence of infection
A positive result of at least one of the following:
Antinuclear antigen
Rheumatoid factor
Anti-Scl 70 antibody
SS-A or SS-B
Jo-1 antibody
Sedimentation rate (>2 × normal), C-reactive protein

Data from [34, 36, 37].

Patients with scleroderma sine scleroderma and amyopathic dermatomyositis might also meet criteria for undifferentiated CTD-ILD. The study of undifferentiated CTD-ILD is an evolving field and, as such, there are limited published data available. However, if tertiary referral centre estimates of prevalence are correct [4] undifferentiated CTD-associated ILD is either the first or second most common CTD-associated ILD.

Definition of undifferentiated CTD-ILD

As no consensus criteria for undifferentiated CTD are universally agreed upon, several different schemas have been used in the published literature; some by rheumatologists [31, 36, 40] and others primarily by pulmonologists [4, 41, 42]. There are no direct empirical data available in the literature to compare the performance characteristics (*e.g.* sensitivity and specificity) of the alternative definitions. The criteria used by our group in the original paper showing a strong association between undifferentiated CTD and the histopathologic pattern of NSIP in a cohort of "idiopathic" interstitial pneumonias [4], has recently been criticised in an opinion article as overly inclusive and nonspecific [43]. The authors suggest an alternative concept of "lung-dominant CTD". The criteria they propose would include all histopathological subtypes of IIP and would require the presence of autoantibodies and/or histopathological features they believe to be specific for CTDs. The main differences between these criteria and the ones we had previously proposed for undifferentiated CTD-ILD are the following: the inclusion of all IIP subtypes, removal of sedimentation rate and C-reactive protein as surrogate laboratory evidence of autoimmunity, and the addition of histopathological features as alternatives to the presence of autoantibodies. Unfortunately, these proposed criteria have not been validated in any existing dataset to establish their performance characteristics, association with clinically meaningful parameters or usefulness. Alternatively, when our criteria for undifferentiated CTD-ILD were applied to existing cohorts of well-characterised patients, they have been shown to be associated with specific radiological and histopathological patterns [4], short-term functional outcomes [44] and even mortality [42].

In selecting among diagnostic criteria for a given condition, the clinician needs to consider contextual features. In screening tests, one often seeks to maximise the sensitivity of the test to avoid missing cases that may benefit from intervention. In doing so, one may be willing to compromise some degree of specificity. This is particularly true if alternative diagnoses do not have particularly effective therapies (such as IPF). Misclassifying a patient as having IPF instead of NSIP (or undifferentiated CTD-ILD) commits the patient to a pessimistic prognosis and may prevent some clinicians from offering potentially effective therapy. In contrast, a patient incorrectly diagnosed as undifferentiated CTD-ILD instead of IPF may be exposed to ineffective therapy but is unlikely to experience substantial harm if monitored carefully.

I do not think that our initial criteria necessarily represent the best possible diagnostic definition of undifferentiated CTD-ILD. Indeed, they were chosen for a specific study based on the types of

data available in the dataset, and were intentionally more sensitive at the cost of some specificity. However, future iterations of diagnostic criteria for undifferentiated CTD-ILD (or ILD with autoimmune features) should be rigorously compared to our prior definition with empiric data that considers important clinical outcomes and should not be assumed to be superior based on expert opinion.

Pulmonary manifestations of undifferentiated CTD

The pulmonary manifestations of large rheumatology based cohorts of undifferentiated CTD have not been well described. A study of 130 subjects with undifferentiated CTD and features of scleroderma, found that approximately one-third had evidence of either lung fibrosis or pulmonary vascular disease [45]. There is growing information about patients with undifferentiated CTD managed predominantly in tertiary pulmonary/ILD centres [4, 42, 44]. The majority of what will be presented here calls upon personal experience and the limited published literature.

Undifferentiated CTD-associated ILD

Epidemiology and clinical features

The majority of patients with undifferentiated CTD-ILD are females (68%) and nonsmokers (53%) [4]. Mean age of the first pulmonary-related symptom (dyspnoea or cough) is 50 yrs. Typically, the extrapulmonary symptoms such as Raynaud's phenomena precede the onset of the lung disease; but this is not universally the case. Dyspnoea is almost always the presenting lung symptom and is accompanied by a dry cough 80% of the time. The most common systemic symptoms are arthralgias/joint swelling (64%) and Raynaud's phenomenon (61%). Other common findings include: oesophageal symptoms such as gastro-oesophageal reflux (65%) and dysphagia (36%); dry mouth or eyes (29%); recurrent unexplained fever (25%); rash (25%); and morning stiffness (18%). The majority of patients with undifferentiated CTD-ILD have multiple systemic symptoms. In one study, 24 (86%) of the patients had at least two symptoms, while 19 (67%) had at least three systemic symptoms. In particular, it is common for subjects to have both arthralgias and Raynaud's phenomenon [4]. Renal involvement, mucosal ulceration, alopecia and photosensitivity do not appear to be common features in undifferentiated CTD-ILD. Digital clubbing is also an uncommon finding (<10%).

The pulmonary function abnormalities seen in subjects with undifferentiated CTD-ILD are similar to those of other chronic interstitial lung disease and consist of restrictive defects with diffusion capacity for carbon monoxide impairments. Patients frequently have impaired gas exchange and demonstrate alveolar–arterial oxygen gradients and exertional hypoxaemia. The presence of autoantibodies is a defining feature of undifferentiated CTD and antinuclear antibodies (ANA) appear to be the most common. Typically, the titre of ANA (1:80–1:360) tends to be lower than that found in other CTDs, such as scleroderma, but higher than the occasional low grade titre (*i.e.* 1:40) seen in healthy subjects or those with IPF. It is unknown if specific ANA patterns (*e.g.* nucleolar) are more prevalent or predictive of disease course in patients with undifferentiated CTD-ILD. The occurrence of other more ''specific'' autoantibodies, such as that to cyclic citrullinated peptide or double stranded DNA, is not known.

Imaging features

A number of radiographic patterns can be seen on CT imaging including: subpleural reticulation, ground-glass opacification, traction bronchiectasis, consolidation and mosaic perfusion. True radiographic honeycombing appears to be uncommon but can be seen in up to 10% of subjects. When honeycombing occurs, it is often in atypical locations compared to IPF in that the finding can be seen in the anterior and upper lung fields without basilar involvement. The finding of ground-glass opacification, particularly when not immediately adjacent to reticular opacities, can

be highly suggestive of an underlying histopathology of NSIP. However, because of the limitations in specificity of any given radiographic pattern when viewed in isolation, one should always consider the clinical context and features before attributing any given finding a histopathologic correlate (figs 1 and 2).

Histopathology

As is seen in other CTDs meeting established ACR criteria [24, 27, 29], such as scleroderma, NSIP has been identified as the most common histopathological pattern found in patients with undifferentiated CTD [4]. In fact, when the criteria for undifferentiated CTD were applied to a cohort of ILD subjects previously considered to be idiopathic in origin, the majority (88%) of persons with the histopathology of NSIP had consistent clinical and serological features [4]. However, it should be noted that there are some patients with undifferentiated CTD that have histopathologic patterns of predominantly organising pneumonia, non-classifiable fibrosis, or even UIP-like patterns. The same is also true of other CTDs [24, 27, 29]. Thus, the pathological finding of NSIP should alert the clinician to the possibility of CTD, but in and of itself are not definitive for CTD.

Diagnostic approach

The initial evaluation of patients with undifferentiated CTD-associated ILD includes high-resolution CT and pulmonary function testing, including diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) (fig. 3). These tests are used to determine the extent and severity of disease, and the magnitude of impairment in lung function. It is important to establish a baseline for these radiographic and functional parameters prior to initiating therapy. We regularly send a comprehensive panel of serum autoantibodies when evaluating patients with incipient ILD, including ANA, rheumatoid factor (RF), anti-Scl-70, anti-tRNA synthetase antibodies (*e.g.* Jo-1, PL-7, PL-12, EJ and OJ), anti-Ro (SS-A), anti-La (SS-B), anti-ribonucleoprotein and anti-cyclic citrullinated peptide. Bronchoalveolar lavage is controversial and not necessarily regularly warranted except to rule out infection. At present, we routinely recommend lung biopsy if an alternative diagnosis such as chronic hypersensitivity pneumonitis is considered. The underlying histopathological pattern may provide some prognostic and therapeutic benefits. For instance, if a UIP-like pattern is seen then the prognosis is likely worse and response to immunosuppressive treatment may be less likely. Decrements in serial pulmonary function tests, particularly forced vital capacity (FVC) or $D_{L,CO}$, are probably the best indicators of progressive disease and a worse prognosis. We use these parameters based on extrapolation from evidence in IPF [46].

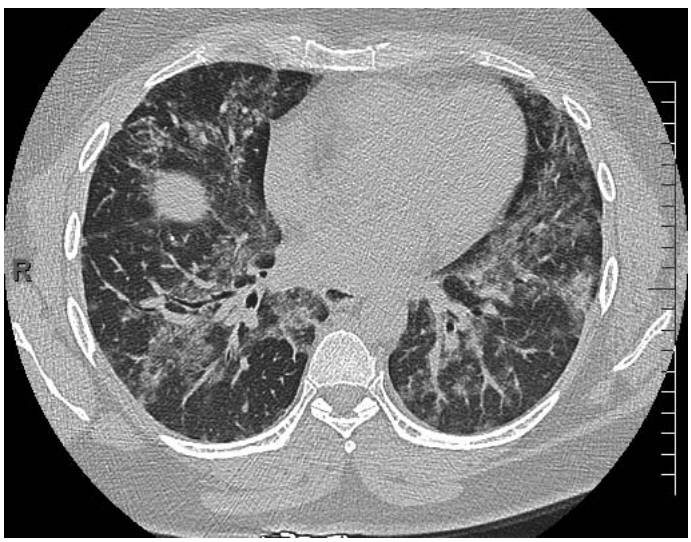

Figure 1. A representative computed tomography scan of the chest from a patient with undifferentiated connective tissue disease.

Outcomes

The clinical and managerial implications of having a diagnosis of ILD superimposed on an underlying CTD may depend upon the underlying CTD. In systemic sclerosis, ILD has surpassed renal involvement as the most common cause of death [12]. Patients with PM/DM-associated ILD have been shown to have significantly better survival

compared to patients with IPF [29]. However, retrospective studies comparing patients with CTD-associated ILD to patients with IIP found that after adjusting for age and other important clinical covariates, there were similar 2- and 5-yr survival rates for the two groups [47, 48]. In a more recent large study, IPF patients were found to have much worse outcome compared to subjects with CTD-associated ILD [49].

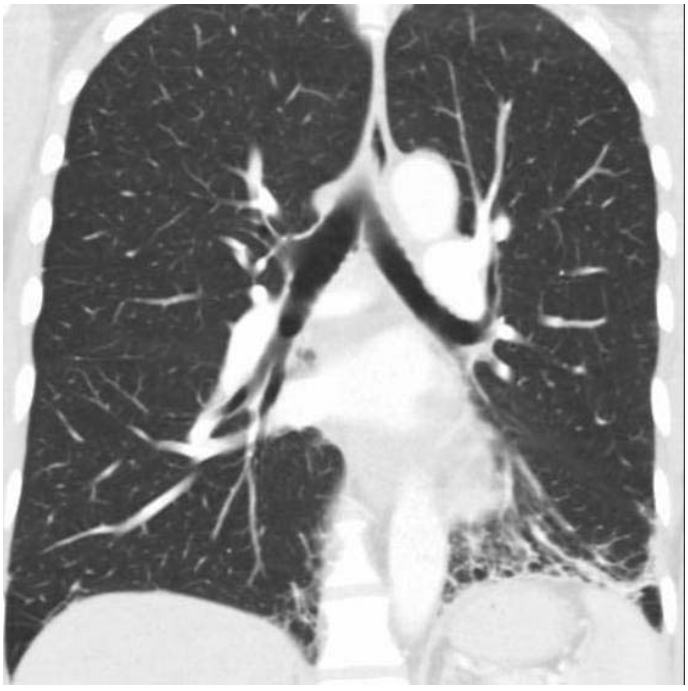

Figure 2. A representative image of a computed tomography scan of the chest from a patient with undifferentiated connective tissue disease showing basilar distribution of the disease.

In a recent retrospective cohort study, 29 patients with undifferentiated CTD-ILD were followed for a median of 8 months with baseline and follow-up pulmonary function tests. During follow-up, 38% of undifferentiated CTD-ILD patients improved ($\geqslant$5% increase in FVC % predicted), 34% stabilised and 28% declined ($\geqslant$5% decrease in FVC % pred) in lung function [44]. This study showed that patients with undifferentiated CTD-ILD had a more favourable clinical course than patients with IPF, as measured by change in FVC, a parameter associated with increased mortality in patients with IPF [50]. It should be noted that almost all of the undifferentiated CTD-ILD subjects had received immunomodulatory agents (cyclophosphamide, azathioprine or mycophenolate mofetil) and/or corticosteroids. There are no available controlled data to determine if the natural course of undifferentiated CTD-ILD is such that there are some individuals with spontaneous improvement in lung function without therapy or if immunomodulatory therapy is necessary.

Pulmonary vascular disease

One study of subjects with undifferentiated CTD and features of scleroderma, found that ~4% had evidence of pulmonary hypertension [45]. In addition, many subjects with advanced ILD develop hypoxaemia-associated pulmonary hypertension later in their disease course. There are no good data on the response to vasodilator therapy in subjects with undifferentiated CTD-associated pulmonary hypertension alone or associated with ILD in combination.

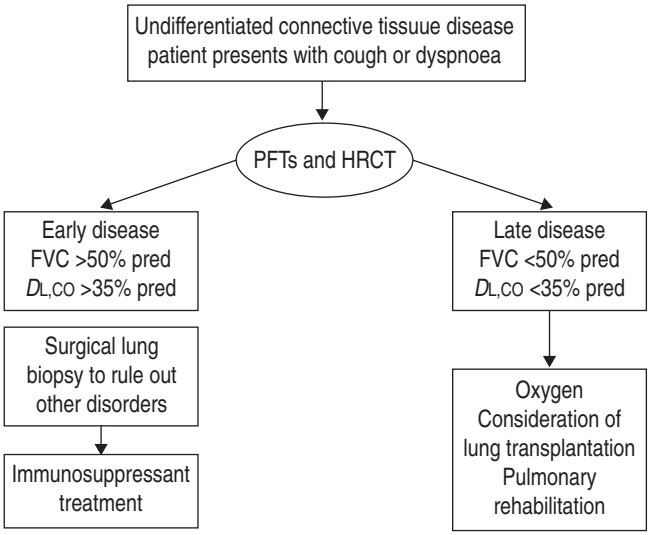

Figure 3. Management algorithm for patients with undifferentiated connective tissue disease. PFT: pulmonary function testing; HRCT: high-resolution computed tomography; FVC: forced vital capacity; % pred: % predicted; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide.

Why does making a diagnosis of ILD with autoimmune features matter?

It is important to diagnose ILD with an autoimmune aetiology for several reasons. First, the recognition of a potential underlying CTD probably improves prognostic estimation for individual patients. As outlined previously, the best data from the literature suggests that the majority of patients with CTD-associated ILD can expect to live for $\geqslant$10 yrs after diagnosis, compared to a median of 4 yrs for patients with IPF [49]. Secondly, there are important therapeutic implications based on appropriate classification. IPF does not appear to be effectively treated with immunomodulatory therapy [51]. Whereas a substantial portion of patients with CTD-ILD will demonstrate significant improvement in lung function when treated with immunosuppression [44, 52]. Finally, recognition of a possible autoimmune aetiology of ILD may allow researchers to investigate novel mechanisms and pathways for future improvements in clinical care [53].

Diagnostic barriers

Although most pulmonologists/respiratory specialists see patients in whom they suspect an underlying autoimmune mechanism as the cause of the pulmonary disease, confirming systemic autoimmune disease and diagnosing specific CTDs in the absence of classic clinical presentations are difficult. Many pulmonologists do not have extensive training or experience in examining the extrathoracic manifestations of systemic autoimmune diseases such as the skin exam, joint exam or neurological exam. Furthermore, there is no consensus regarding appropriate screening laboratory tests. ANA and RF are most frequently requested as CTD screening tests, but these tests probably lack sensitivity and specificity to suffice. Rheumatological classification schemes for the CTDs are based on extrathoracic symptoms and signs and the presence of ''specific'' serologic autoantibodies. Although ILD is a frequent manifestation of CTD, it is not included in the diagnostic criteria for any of the CTDs except as a minor criterion for systemic sclerosis (scleroderma). Consequently, many rheumatologists do not focus on the lung when classifying patients. The net effect of these barriers to a diagnosis of CTD-related ILD is clinical misclassification of the ILD as being of idiopathic nature. This error in classification may prevent patients from receiving appropriate prognostic information or potentially effective therapy.

Multi-disciplinary collaboration

Given the previously discussed challenges in diagnosis, it is imperative for specialists from pulmonology and rheumatology to have on-going communication regarding patients with ILD and autoimmune features. From personal experience, frequent interactions between these specialties regarding the management of specific patients leads to improved awareness and consensus regarding classification. In addition, multi-disciplinary collaboration fosters a more completely integrated management and treatment plan. In much the same way that ILD specialists benefit from face to face interaction with pathologists and radiologists [54], they also benefit from regularly scheduled case discussions with rheumatologists.

Management

The decision to begin treatment in a given patient is complex and must take into account several factors. The disease course of undifferentiated CTD-associated ILD is believed to be heterogeneous with some patients having stable disease for periods of time without treatment and others experiencing rapid deterioration. It is difficult to prospectively identify which patients will have a chronic stable course and which will have progressive disease.

Patient selection

A careful risk-benefit analysis for each patient is necessary when making decisions about who to treat since few ILD treatments have been rigorously studied in randomised controlled trials and

the available treatments are potentially toxic. Generally, we recommend treatment for those patients who have mild-to-moderate symptomatic and physiologic impairment. Based on our clinical experience we believe that this population is likely to progress and has not yet reached the end stage of fibrosis when treatment with immunomodulators is unlikely to reverse the process. In patients who are discovered incidentally (and are asymptomatic) to have ILD, the decision to start treatment is more complicated as some patients may not necessarily progress to symptomatic disease.

Treatment regimen

There are several different regimens that have been used in undifferentiated CTD-associated ILD. The most common of these in our experience and in the published literature will be presented. Most of the well-performed studies for treatment in CTD-ILD are in the scleroderma population.

Corticosteroids and azathioprine

When used in conjunction with azathioprine, the typical starting dose of prednisone (or an equivalent dose of prednisolone) is 0.5 $mg \cdot kg^{-1} \cdot day^{-1}$ given as a single daily oral dose (based upon the patient's ideal body weight and not exceeding 40 $mg \cdot day^{-1}$). If the patient continues to remain stable or improves, the dose is progressively reduced over 3–6 months to 10 $mg \cdot day^{-1}$. This dose is maintained for as long as the treatment appears indicated. For azathioprine, it is recommended to begin with 0.5 $mg \cdot kg^{-1} \cdot day^{-1}$ and gradually increase to a target dose of 2–3 $mg \cdot kg^{-1} \cdot day^{-1}$ given orally as a single dose. A discernible response to therapy may not be evident until the patient has received treatment for 3–6 months.

It should be noted that rheumatologists are often cautious in using corticosteroids in patients with scleroderma because of concern regarding the possibility of precipitating renal crisis [55]. This concern is based upon observational data suggesting an increased risk of renal crisis with use of prednisone doses >15 $mg \cdot day^{-1}$. This association could be the result of confounding by indication (*i.e.* more severely affected patients were also more likely to receive higher dose) or a true causal factor. Regardless, caution is warranted when using steroids in systemic sclerosis-ILD patients, with close monitoring of renal function and early institution of angiotensin converting enzyme inhibitors, if necessary.

Cyclophosphamide ± corticosteroids

Cyclophosphamide has been well studied in scleroderma lung disease but less so in other CTD-associated ILDs. A National Institute of Health sponsored multicentre clinical trial (the Scleroderma Lung Study) assessed the efficacy and safety of oral cyclophosphamide in scleroderma-associated ILD [52]. This was a randomised, placebo-controlled trial of 162 patients with early scleroderma-associated ILD (defined by the presence of ground-glass opacities on high-resolution CT or bronchoalveolar lavage fluid with elevated neutrophils or eosinophils) to receive either oral cyclophosphamide (initial dose of 1 $mg \cdot kg^{-1} \cdot day^{-1}$ increased to a maximum of 2 $mg \cdot kg^{-1} \cdot day^{-1}$ as tolerated) or placebo. The concurrent use of glucocorticoids (up to 10 $mg \cdot day^{-1}$ prednisone) was permitted. At the end of 12 months of therapy, the mean change in FVC, the primary outcome measure, showed a significantly smaller decline in patients who received cyclophosphamide compared to those on placebo (-1.4% *versus* -3.2%). There were more adverse events (haematuria, leukopenia, neutropenia and pneumonia) in the cyclophosphamide treated group. There are concerns about the long-term adverse events in the cyclophosphamide treated group, such as bladder malignancy that may not become clinically evident until years after treatment. Treatment with high cumulative cyclophosphamide doses have been shown to lead to a substantial risk of late-occurring serious malignancies in granulomatosis with polyangiitis (Wegener's) patients. In a large

population-based Danish study, patients treated with the equivalent of 100 mg of cyclophosphamide per day for >1 yr had a 20 times increased risk of acute myeloid leukaemia and 3.5 times increased risk of bladder cancer within 7–19 yrs after therapy compared to the general population [56]. In a US-based study of patients with granulomatosis with polyangiitis (Wegener's) who were treated with cyclophosphamide, the estimated incidence of bladder cancer after the first exposure was 5% at 10 yrs and 16% at 15 yrs [57]. The side-effect profile and potential increase in long-term risk of malignancy coupled with the modest clinical benefit of the intervention argue against the routine use of this regimen in CTD patients.

Mycophenolate mofetil ± corticosteroids

There are no controlled trials published with this regimen. Recently, however, several major academic clinical centres have been using mycophenolate mofetil ± corticosteroids in the treatment of CTD-associated ILD. In a retrospective study of 28 patients with CTD-associated ILD, side-effects occurred in six patients but improved with dose reduction [58]. In addition, the patients had modest improvements in pulmonary function tests (average change in FVC 2.3% pred, total lung capacity (TLC) 4.0% pred and $D_{L,CO}$ 2.6% pred). It should be noted that there is also a theoretical increased risk of malignancy associated with use of mycophenolate, although this has not been well established in the literature.

Assessing the response to therapy

The response to therapy should be assessed 3–6 months after its initiation. A favourable response to therapy is often defined by: a decrease in symptoms, especially dyspnoea and cough; physiologic improvement assessed by FVC, TLC, $D_{L,CO}$, and both resting and exercise gas exchange; and stabilisation of lung function, radiographic abnormalities and symptoms.

Frequently, some parameters improve while others decline or are unchanged. Subjective improvement can occur in some patients who have no objective signs of improvement. In general the subjective response should not be the only factor in determining whether to continue treatment.

The following findings are considered to represent failure of therapy and are an indication to modify the treatment regimen: a reduction in FVC or TLC by $\geq$10%; worsening of radiographic opacities, especially with development of honeycombing or signs of pulmonary hypertension; and decreased gas exchange at rest or with exercise.

Clinical deterioration is most frequently due to disease progression. However, disease-associated complications and adverse effects of therapy should also be considered.

Conclusions

Undifferentiated CTD-ILD (or ILD with autoimmune features) is an increasingly recognised disease entity among centres specialising in research and the care of patients with ILD [4, 42, 59]. Recognition of subtle signs and symptoms of CTD, followed by appropriate laboratory evaluation, are critical for case identification. Multi-disciplinary collaboration between pulmonologists and rheumatologists is critical for disease classification and management. It appears that patients with undifferentiated CTD-ILD may have a better prognosis and response to immunomodulatory treatment than patients with IPF. The proportion of patients with undifferentiated CTD-ILD that evolve to other well-characterised forms of CTD is unknown. Future research should help define the disease course and most effective therapies for patients with undifferentiated CTD-ILD.

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Statement of interest

None declared.

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