



Occult connective tissue diseases mimicking idiopathic interstitial pneumonias

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ABSTRACT: In patients with interstitial lung disease (ILD), the diagnosis of idiopathic interstitial pneumonia is usually made after excluding, among other conditions, connective tissue diseases (CTDs). Although in most patients with a CTD and respiratory symptoms, the systemic nature of the disease is obvious, the ILD-related manifestations in CTDs may often dominate the clinical picture or precede systemic findings and thus mimic idiopathic interstitial pneumonia.

With the exception of systemic lupus erythematosus, all CTDs may imitate chronic idiopathic interstitial pneumonias. In this setting, clues to an underlying CTD may be entirely absent or include subtle findings from various systems, including skin, vascular and musculoskeletal system or internal organs. Since nonspecific interstitial pneumonia is a relatively frequent histological pattern in CTDs, biopsy reports of nonspecific interstitial pneumonia should also prompt a search for an underlying CTD.

Ultimately, diagnosis of a CTD requires confirmation with immunological testing; interpretation of the various laboratory tests should always be carried out in conjunction with clinical findings.

The present article reviews specific clinical aspects of connective tissue disease-related interstitial lung disease that may help differentiate it from idiopathic interstitial pneumonia, especially when interstitial lung disease is the predominant or sole manifestation of an occult connective tissue disease.

KEYWORDS: Connective tissue-related, idiopathic pulmonary fibrosis, interstitial lung diseases

The term idiopathic interstitial pneumonias (IIPs) refers to a heterogeneous group of acute, subacute or chronic interstitial lung diseases (ILDs) characterised by different combinations of inflammation and fibrosis, as well as by a restrictive pulmonary defect and abnormal gas exchange [1, 2]. The most common form of IIP is idiopathic pulmonary fibrosis (IPF) [3–5]. The IIPs account for a substantial portion, ~25–30%, of all ILDs [6, 7]; the remaining ILDs include various occupational, drug-induced and connective tissue diseases (CTDs), as well as disorders of unknown cause [1].

In the absence of clinical or laboratory tests specific for IIPs, their diagnosis is critically dependent upon the exclusion of certain drug toxicities, environmental exposures and CTDs [1, 2]. Unlike external causative factors that may be suspected from a pertinent exposure or drug history, an occult CTD may occasionally confuse the diagnostic process because the CTD-related respiratory symptomatology may not always be accompanied by systemic manifestations and thus mimic IIP [7, 8].

The present article focuses on specific CTDs that may present solely or predominantly with

chronic ILD-related symptoms. Since such patients are often seen by a non-rheumatologist, the present article is intended to help the clinician suspect an underlying CTD as the cause of ILD in the occasional patient with respiratory symptoms and no apparent systemic involvement. It does not deal with the wide spectrum of respiratory manifestations related to CTD, as in-depth reviews devoted to this topic can be found elsewhere [9–11].

CTD MIMICKING IIP: PREVALENCE AND SIGNIFICANCE OF EARLY DIAGNOSIS

The most frequent types of ILD encountered in patients with CTD are nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), acute interstitial pneumonia, cryptogenic organising pneumonia (COP) and lymphocytic interstitial pneumonia (LIP; table 1) [9, 12–16]. By and large, these entities exhibit similar radiological and histological characteristics to their idiopathic counterparts and are thus considered indistinguishable [15, 17–19]. Despite similarities in histological and radiological profiles, there are significant differences in survival between the two groups. Patients with CTD-related ILD survive longer than those with IIP [20–23]. The

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STATEMENT OF INTEREST

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TABLE 1 Types of interstitial lung disease encountered in connective tissue diseases

	SSc	PM/DM	PSS	RA	SLE	MCTD
Usual interstitial pneumonia	++	++	+	++	+	+
Nonspecific interstitial pneumonia	++++	++++	+	+	++	++
Cryptogenic organising pneumonia	+	++	+	+	+	-
Diffuse alveolar damage	+	++	+	+	++	-
Lymphocytic interstitial pneumonia	-	-	+++	-	-	-

SSc: systemic sclerosis; PM: polymyositis; DM: dermatomyositis; PSS: primary Sjögren's syndrome; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; MCTD: mixed connective tissue disease. +: lowest frequency; ++++: highest frequency; -: rare pulmonary involvement. Reproduced and modified from [12] with permission from the publisher.

difference appears to be related to a better survival of patients with CTD-related UIP rather than to the higher prevalence of NSIP in CTDs [22].

Specific types of CTD-related ILD may present with a fulminant picture and mimic acute respiratory distress syndrome [24]. Although acute presentation of ILD may occur with any CTD, it is more common in systemic lupus erythematosus (SLE) and polymyositis (PM) dermatomyositis (DM), followed by mixed CTD and rheumatoid arthritis (RA).

It is estimated that up to 15–20% of patients who present with a chronic ILD either have an occult CTD [15] or subsequently develop a clinically overt CTD. In this particular group of patients, the initial clinical presentation may be essentially indistinguishable from that of IIP [15, 18]. Reporting on 68 patients with IIP followed-up for a period ranging 1–11 yrs, HOMMA *et al.* [18] reported on 13 (19%) patients who subsequently developed a CTD. Initial laboratory findings such as levels of antinuclear antibody (ANA) or rheumatoid factor (RF) did not differ between those who did and did not develop a CTD.

How often is CTD-related ILD misclassified as IPF? In a group of patients diagnosed with IPF, FISCHER *et al.* [25] recently assessed the prevalence of antibodies considered highly specific for scleroderma (those directed against Th/To ribonucleoprotein (anti-Th/To), or ANA with nucleolar staining). In the entire IPF group, ~9% of patients were found to have one or both types of these antibodies and thus diagnosed as having scleroderma sine scleroderma [25]. Indeed, on retrospective evaluation, most patients with the nucleolar ANA staining, and especially those with positive anti-Th/To antibodies, met criteria for scleroderma sine scleroderma.

Findings favouring CTD-related ILD over IIP are the presence of pleural effusion or significant pleural thickening [26]. Also, biopsy reports consistent with NSIP should raise suspicions about the possibility of an underlying CTD because of the high prevalence of NSIP in CTDs [16, 17, 27–30]. Other biopsy findings that may be suggestive of an underlying CTD include

follicular bronchiolitis and lymphoid follicles or pleural lymphoplasmacytic infiltration [16].

In patients presenting with ILD, prompt diagnosis of an occult CTD is crucially important for several reasons. First, it helps the clinician choose the appropriate therapeutic regimen. NSIP related to scleroderma, for example, may require a different therapeutic regimen from the idiopathic form of the disease [31, 32]. Recent data have shown that, in patients with scleroderma-related ILD, oral cyclophosphamide given for 1 yr results in significant improvements in dyspnoea and health-related quality of life, and modest increases in forced vital capacity and total lung capacity [31]. Owing to the systemic nature of CTDs, a search for additional system involvement (*i.e.* cardiac in scleroderma) or underlying malignancy (*i.e.* PM/DM) might also be needed in some cases [20]. Additional advantages of an early diagnosis are fewer diagnostic tests and no need for open lung biopsy when diagnosis is established on the basis of clinical, radiological and laboratory (highly specific autoantibodies) data. Finally, diagnosis of a CTD in this setting enables the clinician to better define disease prognosis and alert the patient about specific complications (*i.e.* respiratory muscle involvement in PM/DM).

Table 2 illustrates specific CTDs in which chronic ILD may be the sole or predominant manifestation. The clinical characteristics of these diseases are briefly highlighted below. ILD may also occur in SLE. However, the ILD in SLE is typically accompanied by other systemic disease manifestations and does not usually cause diagnostic problems [9, 10, 33, 34].

POLYMYOSITIS/DERMATOMYOSITIS

PM/DM are idiopathic inflammatory myopathies characterised by inflammation and weakness of skeletal muscles, associated, in the case of DM, with characteristic skin manifestations [35].

ILD is one of the major extramuscular manifestations of the disease, occurring at a frequency ranging 5–64% of patients [20, 36–38]. Although NSIP is the most common pattern [16, 20, 36, 38], COP, diffuse alveolar damage and UIP are also frequently found [16, 20, 36, 38–40]. The diagnosis of PM/DM-related ILD does not pose a diagnostic challenge in patients with established disease or in newly diagnosed patients with typical disease manifestations. However, PM/DM may not be suspected as the underlying cause of ILD when lung involvement is the sole manifestation [20, 38, 41] or when muscle weakness is obscured by incapacitating dyspnoea [20, 38, 42]. Rarely, in patients with amyopathic DM, the ILD may

TABLE 2 Connective tissue diseases whose interstitial lung disease may mimic chronic idiopathic interstitial pneumonia

Polymyositis/dermatomyositis
Scleroderma
Rheumatoid arthritis
Sjögren's syndrome
Mixed connective tissue disease
Undifferentiated connective tissue disease

also create diagnostic difficulties due to the absence of muscle weakness [43].

ILD as the sole PM/DM manifestation

ILD can be the presenting manifestation in a significant percentage of patients with PM/DM, with other disease symptoms and signs being minimal or entirely absent [17, 18, 20, 38, 44]. In a series of 70 patients with PM/DM and ILD reported by DOUGLAS *et al.* [20], ILD was the sole manifestation in 21 (30%) patients. In an additional 15 patients, there were synchronous respiratory and muscular/cutaneous signs and symptoms. Similar findings were also reported by MARIE *et al.* [38] in a series of 36 patients with PM/DM-related ILD, with ~20% of patients initially presenting with lung disease.

Patients initially presenting with only respiratory complaints often have crackles on lung auscultation, and complain of weakness and arthralgias [20]. Joint involvement, particularly in the form of arthralgias, occurs more frequently in patients with ILD than in those without lung involvement [38, 45]. The diagnosis of PM/DM can be delayed for months or even years after the initial diagnosis of ILD, especially when corticosteroids are used [20, 45].

ILD and amyopathic dermatomyositis

Amyopathic DM is a discrete subgroup of DM characterised by skin manifestations typical of DM but without muscle weakness [46]. Muscle involvement may never occur [46] or manifest months after the initial skin disease [47]. Although ILD does not usually precede the skin manifestations of DM, the underlying ILD diagnosis may be missed if proper attention is not paid to skin rash [43].

The prevalence of ILD in amyopathic DM ranges 10–20% [47, 48]. In a meta-analysis of 291 cases of amyopathic DM [47], 13% of patients had ILD. In six patients with amyopathic DM, KRAIN [48] found two patients with pulmonary fibrosis in whom pulmonary fibrosis had contributed to delay in diagnosis. In a study involving 14 patients with ILD and amyopathic DM, SUDA *et al.* [43] described two types of ILD, an acute/subacute type with a relatively high mortality and a chronic type. In its rapidly progressive form, the disease may present as diffuse alveolar damage, refractory to high-dose steroids and with a high mortality rate [43, 49, 50].

Antisynthetase syndrome

Antisynthetase syndrome refers to a particular group of PM/DM patients who have specific autoantibodies called antisynthetases. These antibodies are directed against synthetases, the cytoplasmic enzymes facilitating attachment of amino acids to their correspondent transfer RNAs (tRNAs). Clinical characteristics of the syndrome include myositis, Raynaud's phenomenon, fever, mechanic's hands and arthralgias [51–53]. With an incidence ranging 75–100% [51, 54, 55], ILD does not differ in presenting symptoms and histological appearance from ILD of other aetiologies, and is the main cause of morbidity and mortality in these patients [56].

Of all antisynthetase antibodies, one directed against histidyl transfer RNA synthetase (anti-Jo-1) is the most commonly detected. Since these antibodies are very specific, their presence is of high diagnostic significance. This can be especially helpful

in cases in which one or more of the clinical manifestations of antisynthetase syndrome do not temporally coincide with ILD (fig. 1) [53, 57–59]. In some cases [55, 58], myositis may follow years after autoantibody detection, whereas, in others, no clinical myositis ensues during the observation period [53]. In patients with less common antisynthetases (*i.e.* directed against alanyl tRNA synthetase (PL-12)), ILD may be the sole manifestation of the syndrome [57].

SCLERODERMA

Scleroderma or systemic sclerosis (SSc) is a multisystemic disease of unknown aetiology characterised by fibrosis of the skin and internal organs [60]. Associated more often with the diffuse than the limited form of SSc, ILD is one of the major causes of SSc-related mortality. Although the overall prevalence of ILD varies depending upon the method used and population studied, its estimated range is 70–80% [61–63]. The diagnostic challenge of ILD-related SSc lies in the fact that skin involvement, which is the trademark of the disease, may be either entirely absent (scleroderma sine scleroderma) or very subtle, as may occur in some forms of limited scleroderma with anti-Th/To antibodies.

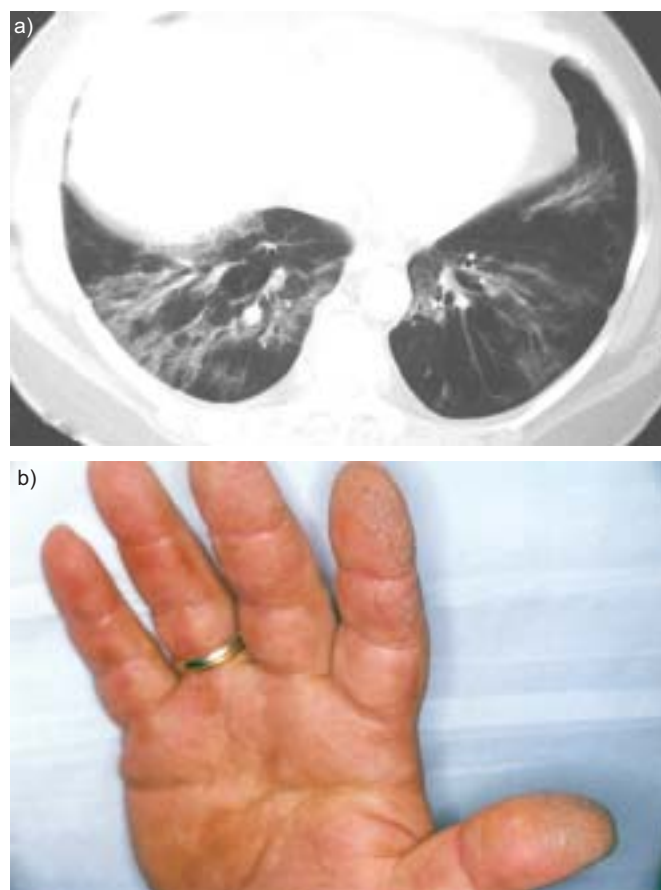


FIGURE 1. a) Lung computed tomography of a patient with antisynthetase syndrome and histidyl transfer RNA synthetase (Jo-1) antibodies. The patient presented with dyspnoea and cough; the correct diagnosis was made with a 6-month delay, when the patient developed the characteristic hand rash (mechanic's hands; b).

Scleroderma sine scleroderma

In this particular group of SSc patients, ILD may occur without skin thickening and may be the predominant or sole manifestation [32, 64–67].

Originally described by RODNAN and FENNELL [68] >40 yrs ago, scleroderma sine scleroderma is essentially a variant of limited scleroderma with an estimated prevalence of approximately one tenth of that of the limited disease subtype [69]. ILD occurs in >80% of patients with scleroderma sine scleroderma and may be confused with IPF. The histological and radiological features are those of NSIP (fig. 2) or UIP [32]. The clinician may suspect the entity by certain characteristic findings suggestive of systemic involvement. Most patients show scattered telangiectasias, Raynaud's phenomenon, oesophageal reflux disease, abnormal nail capillaroscopy or asymptomatic pericardial effusion on echocardiographic examination [32, 65]. ANAs are found in the majority of cases (>93%) [32, 69], with the most frequent type being non-SSc-associated autoantibodies followed by anticentromere antibodies; anti-topoisomerase I or anti-Th/To may be detected less frequently [69]. Reporting on 48 patients with scleroderma sine scleroderma, POORMOGHIM *et al.* [69] have suggested that the disease should be considered in the presence of the following features. 1) Raynaud's phenomenon or a peripheral vascular equivalent, such as digital pitting scars, digital tip ulcers, digital tip gangrene or abnormal capillaries. 2) Positive ANA results. 3) Any one of the following: distal oesophageal hypomotility, small bowel hypomotility, pulmonary fibrosis, pulmonary arterial hypertension without fibrosis, cardiac involvement typical of scleroderma, or renal failure consistent with sclerodermic renal crisis, and no other CTD or disease that would explain these findings.

Limited scleroderma with antibodies directed against Th/To ribonucleoprotein

In some patients with limited scleroderma, the presence of anti-Th/To antibodies may be associated with minimal skin

thickening and relatively less prominent vascular disease. These two clinical features occur comparatively less than in the classic form of limited scleroderma. Pulmonary fibrosis is seen more frequently than in anticentromere-positive patients (48 *versus* 13%) and is the second most common cause of death in these patients [70]. Owing to subtle skin changes, the diagnosis of scleroderma can be easily missed in patients presenting with ILD-related symptoms [70].

Anti-Th/To antibodies are directed against a group of RNA processing enzymes [71] and occur in 4–13% of SSc patients, mostly in those with limited disease [70, 72]. Although testing for anti-Th/To antibodies is not commercially available, their presence may be a useful marker for underlying scleroderma sine scleroderma in a patient with ILD [32]. On ANA staining, they produce a bright nucleolar or nucleolar plus speckled pattern. As with scleroderma sine scleroderma, the diagnosis should be suspected in patients with Raynaud's phenomenon, telangiectasias, digital tip ulcers, oesophageal hypomotility, cardiac involvement and a positive ANA result with a bright nucleolar or nucleolar plus speckled pattern [70].

RHEUMATOID ARTHRITIS

RA is a systemic autoimmune disorder characterised by widespread joint inflammation with synovial hyperplasia. The disease affects 1–2% of the population and is frequently associated with extra-articular manifestations in the skin, eye, heart and lung [73, 74].

ILD is the commonest and most serious pulmonary complication of RA; it affects ~15–20% of patients with RA, although higher prevalence rates are reported when different methods of detection are employed [13, 75–79]. The most prevalent histological pattern is UIP followed by NSIP; COP may also occur but less frequently [13, 14, 79, 80].

In ~90% of RA patients, ILD poses no diagnostic difficulties because it follows the onset of joint symptoms by a few years [75, 81]; in some cases, joint involvement, albeit present, might be overlooked due to decreased mobility related to pulmonary impairment. However, in ~10% of cases, ILD may be the first manifestation of RA, especially that with the histological pattern of NSIP [10, 79, 82]. In this setting, the aetiological diagnosis of ILD is difficult and indistinguishable from that of IIP. In a small proportion of RA patients with ILD but no joint involvement, subcutaneous nodules may be present and suggest the presence of a systemic disease. In a study of 18 patients with RA-related ILD reported by LEE *et al.* [82], ILD preceded RA diagnosis in three patients by 1.6, 2.5 and 7 yrs, respectively, whereas, in another three patients, the diagnosis of ILD and RA occurred simultaneously.

Detection of cyclic citrullinated peptide (CCP) antibodies, which has recently become available, may help diagnostically in cases in which ILD precedes the arthritic manifestations of RA. These antibodies are directed against the citrullinated proteins, such as fillagrin and its circular form, CCP. Anti-CCP antibodies are detected in the serum of asymptomatic blood donors years before the clinical diagnosis of RA is made [83]. Also, in patients with early undifferentiated arthritis, anti-CCP antibodies are very strong predictors for subsequent development of RA and joint destruction [84]. Owing to their high specificity and sensitivity, especially when combined with

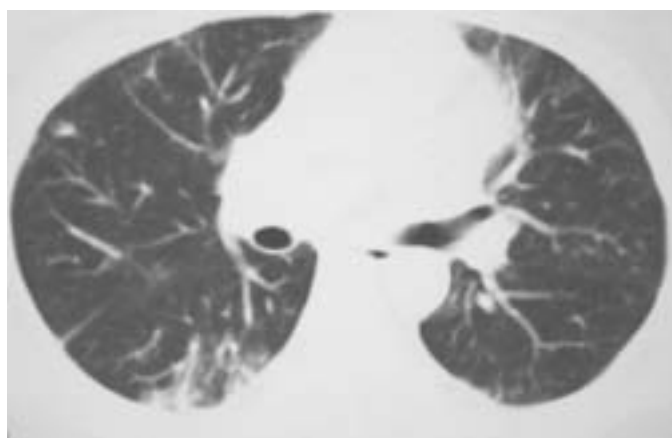


FIGURE 2. Lung computed tomographic appearance of biopsy-proven nonspecific interstitial pneumonia (NSIP) in a patient with scleroderma sine scleroderma. The patient, who had history of oesophageal reflux disease, presented with dyspnoea on exertion. The initial diagnosis was idiopathic NSIP; within the ensuing year, the patient developed Raynaud's phenomenon and an asymptomatic pericardial effusion. Laboratory testing revealed antinuclear antibody (dilution 1/1,280) with a nucleolar pattern.

positive RF results, anti-CCP antibodies may become a useful tool for establishing a diagnosis of RA.

SJÖGREN'S SYNDROME

Sjögren's syndrome (SS) is a chronic autoimmune disorder characterised by lymphocytic infiltration of the exocrine glands and epithelium of various organs. A primary, or secondary in conjunction with other autoimmune diseases, disorder, SS occurs in 0.1–1% of the population [85, 86]. Respiratory system involvement in primary SS mainly manifests as small airway disease, large airway obstruction or desiccation of the tracheobronchial tree [87, 88].

ILD may also occur in primary SS (fig. 3) but less frequently than the airway manifestations [13]. Although its exact prevalence is not known, it is probably <5% [13, 89–91]. Early studies considered LIP and primary pulmonary lymphoma as the most common forms of parenchymal disease in primary SS, whereas UIP and NSIP were considered rare. However, recent studies [91, 92] have reported that NSIP and, less frequently, UIP may also occur in primary SS. ITO *et al.* [92] reported that NSIP was the most common histological pattern, found in 60% of patients with SS and ILD. In a similar study involving 18 patients with primary SS and ILD [91], NSIP was also the predominant histopathological type, followed by UIP and LIP. Notably, in the study of ITO *et al.* [92], no case with a histological LIP pattern was detected.

Although exceedingly rare, the patient with primary SS may present with radiological and physiological findings consistent with ILD but without prominent sicca symptoms [88]. This occurs especially frequently in older patients, who tend to dismiss sicca symptoms as age-related. In this case, specific questioning regarding sicca-associated symptoms should be sought or a specific sicca-associated questionnaire should be filled in by every patient presenting with ILD. If clinically suspected, the diagnosis of ILD–SS can be established by specific tests, including lip biopsy and serology. These patients almost invariably exhibit positive ANA results; specific autoantibodies, such as anti-SSA and anti-SSB, are also detected in 70–90% of cases [91].

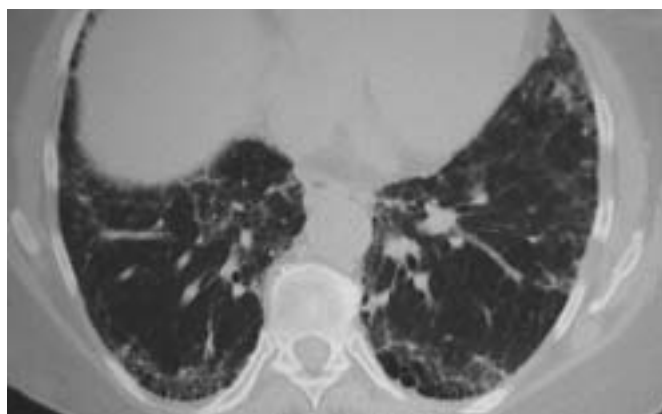


FIGURE 3. Thoracic computed tomography showing a usual interstitial pneumonia pattern in a patient with Sjögren's syndrome and interstitial lung disease. The patient presented with dyspnoea and cough; sicca symptoms were also present.

MIXED CTD

Mixed CTD (MCTD) is a disease characterised by overlapping features of SLE, SSc and PM, and high titres of autoantibodies directed against U1 small nuclear ribonucleoprotein (RNP). Common clinical features include Raynaud's phenomenon, swollen hands, arthritis, sclerodactyly, myositis and ILD; pulmonary hypertension and pleural effusions may also occur [93–95].

ILD is estimated to occur in up to 65% of patients with MCTD [95]; its major histopathological pattern is that of NSIP, as suggested by histological and radiological data [12, 22, 96]. It typically manifests within the first 2–4 yrs following disease onset, when other systemic manifestations of SLE, SSc or PM are also present as the disease progresses [93, 95]. Rarely, the ILD-related symptoms may be the predominant or first manifestation of the disease [96]. In a group of 35 patients with MCTD and ILD undergoing thoracic imaging, SAITO *et al.* [96] reported three patients with only respiratory problems, who were initially believed to have IPF but later diagnosed with MCTD.

In the majority of MCTD-related ILD cases, there appears to be no diagnostic difficulty in identifying the systemic nature of the illness. In the rare case in which ILD symptomatology predominates the clinical picture, the high titre of anti-RNP (dilution >1:1,600) provides a clue to the disease [97].

UNDIFFERENTIATED CTD

Undifferentiated CTD (UCTD) includes those patients with some clinical and serological characteristics suggestive of autoimmune disease, yet insufficient to make a diagnosis of a specific CTD [98, 99]. These patients may not necessarily progress to a specific CTD [98, 99]. Nonpulmonary symptoms may be subtle and include arthralgias or arthritis, Raynaud's phenomenon and haematological abnormalities, including anaemia or leukopenia, and sicca symptoms [98, 99]. Of the patients, ~90% are ANA-positive and, in the majority of cases, there is single antibody positivity, usually of anti-SSA/Ro or anti-RNP antibodies [100].

In the absence of diagnostic criteria [98], the diagnosis of UCTD and its aetiological association with ILD can be contentious. It is quite possible that the ILD, in this setting, is misclassified as IIP [101, 102]. In a recent study, KINDER *et al.* [102] assessed the prevalence of UCTD in a group of patients with IIP. Using a predefined set of criteria (*i.e.* combination of clinical and serological markers), they found that ~10% of IIP patients met criteria for UCTD. These patients were typically younger, female and nonsmokers, and, in the majority of them, the histological pattern was NSIP. These findings prompted the authors to propose that the so-called idiopathic NSIP may in fact be the pulmonary manifestation of a generalised autoimmune process.

PHYSICAL EXAMINATION

Review of systems, in conjunction with a comprehensive physical examination, may yield significant clues to an underlying CTD. Table 3 presents symptoms and physical findings commonly associated with CTDs. Raynaud's phenomenon in a patient with ILD invariably indicates an autoimmune disease. Since Raynaud's phenomenon is found

in >90% of patients with scleroderma sine scleroderma, its absence should make this diagnosis less likely [32, 69]. If scleroderma sine scleroderma is suspected, the search for telangiectasias should be thorough and include face, lips, palms and mucous membranes. As with Raynaud’s phenomenon, digital tip ulcers or pitting scars are signs suggestive of vasculopathy. Puffy fingers are frequently seen in patients with occult CTD.

Arthralgias without synovitis may occur in patients with IPF, whereas active arthritis suggests an underlying CTD. Clubbing, which is found in >50% of IPF patients, is also seen in RA-related ILD and less frequently in PM/DM. The characteristic skin rashes of DM include the violaceous scaly patches found over bony prominences, the violaceous (heliotrope) discoloration of eyelids and Gottron’s papules. Mechanic’s hands (fig. 1), which is pathognomonic for antisynthetase syndrome, consists of a thick and fissured skin texture involving the palmar surfaces of both hands.

Gastro-oesophageal reflux disease is present in up to 20% of the healthy adult population [103, 104]. It is very common in

patients with IPF, with the reported prevalence being >80% [105]. Since gastro-oesophageal reflux disease may occur due to underlying scleroderma, special consideration should be given to this symptom, which should not be dismissed as insignificant. For example, in patients with scleroderma sine scleroderma, gastrointestinal involvement occurs in ~80% of patients [32, 69, 105].

LABORATORY FINDINGS

In the patient with ILD and suspicion of an occult CTD, specific laboratory testing tailored to clinical impression is required to rule out a systemic disease. In general, laboratory tests are not highly sensitive or specific for accurate diagnosis of CTDs. However, in conjunction with clinical evidence, these tests may provide a high degree of confidence regarding the presence of a CTD. In addition to routine laboratory testing, such as complete blood count, urinalysis, erythrocyte sedimentation rate and measurement of C-reactive protein and serum immunoglobulins, levels of the muscle enzymes creatine phosphokinase and aldolase should form part of the initial laboratory panel. A comprehensive, but by no means complete, list of laboratory tests is shown in table 4.

Autoantibody testing plays a central role in both screening for and diagnosis of CTDs. Since these tests have limitations and their use may lead to erroneous conclusions, interpretations should always be made in conjunction with the clinical picture. ANAs are usually detected by indirect immunofluorescence after sera incubation with fixed Hep-2 cells. They are useful in the initial screening process and may provide information about the presence of other autoantibodies that need to be detected. The ANA results (titre and pattern) are subjective and may vary between laboratories depending upon experience. In addition to clinical findings, interpretation of a positive ANA test result needs to take into consideration the patient’s age and antibody titre. Positive ANA testing is also associated with infections, drug therapy and various inflammatory diseases. It should be noted that ANA titre is not a marker of disease activity. In general, the higher the titre the more likely it is that a CTD is present. Low ANA titres

TABLE 3 Symptoms and signs associated with connective tissue diseases	
Joint and muscle	
Arthralgias	
Arthritis	
Morning stiffness	
Synovitis	
Myalgias	
Muscular weakness	
Skin	
Raynaud’s phenomenon	
Digital ulcers	
Pitting scars	
Telangiectasias	
Sclerodactyly	
Puffy hands	
Malar rash	
Photosensitivity	
Heliotrope rash	
Mechanic’s hands	
Gottron’s papules	
Subcutaneous nodules	
Gastrointestinal	
Dry mouth	
Mouth ulcers	
Oesophageal reflux or hypomotility	
Dysphagia	
Abdominal bloating	
Ophthalmological	
Dry eyes	
Corneal ulcers	
Uveitis	
Scleritis	
Thoracic	
Pleuritis	
Pericarditis	

TABLE 4 Laboratory evaluation of the patient with connective tissue disease-related interstitial lung disease	
Routine	Complete cell count; electrolytes; blood urea nitrogen; creatinine; liver function tests; urinalysis; CPK; aldolase; ESR; CRP; serum immunoglobulins; ECG; echocardiography
Serological	ANAs with pattern, titre and ENAs; RF; anti-CCP antibody; anti-SSA/SSB antibodies (Ro/La); anti-Scl-70; anticentromere antibody; Jo-1 antibody; anti-Mi-2 antibody; anti-RNP
CPK: creatine phosphokinase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: antinuclear antibody; ENA: extractable nuclear antigen; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; SS: Sjögren’s syndrome; Scl: scleroderma; Jo-1: histidyl transfer RNA synthetase; Mi-2: Mi-2 nuclear antigen; RNP: ribonucleoprotein.	

TABLE 5 Autoantibody prevalences by disease association

	SLE	RA	SSc	PM/DM	PSS	MCTD
ANA	90–98	40	96	25–90	70–95	93
Anti-dsDNA	50–80					
Anti-Smith	20–30					
RF	15–25	65–90	10–50	10–40	30–70	
Anti-SSA/Ro	20–30				50–90	
Anti-SSB/La	10–20				50	
Anti-Scl-70			30–35 [#] 10–20 [*]			
ACA			40–80 [*]			
Anti-Jo-1				10–50		
Anti-RNP	30–40					100
Anti-CCP		50–75				

Data are presented as percentages. SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SSc: systemic sclerosis; PM: polymyositis; DM: dermatomyositis; PSS: primary Sjögren's syndrome (SS); MCTD: mixed connective tissue disease; ANA: antinuclear antibody; dsDNA: double-stranded DNA; RF: rheumatoid factor; Scl: scleroderma; ACA: anticentromere antibody; Jo-1: histidyl transfer RNA synthetase; RNP: ribonucleoprotein; CCP: cyclic citrullinated peptide. [#]: diffuse SSc; ^{*}: limited SSc.

(dilution <1:160) occur in ~10–20% of patients with IPF [101]. In contrast, a negative ANA test result does not necessarily exclude a CTD.

Specific autoantibody testing for an extractable nuclear antigen (ENA) should supplant positive ANA testing. Table 5 shows the most clinically useful specific autoantibodies with their disease associations and prevalence. Of these autoantibodies, anti-SSA/Ro and anti-SSB/La should be determined separately, even in the absence of a positive ANA result, when SS is clinically suspected [106, 107]. The presence of these autoantibodies in the appropriate setting is highly specific for a CTD.

ANA staining patterns are currently less important due to the ability to detect specific ENAs. However, they continue to be relevant since they might provide a clue to the presence of less typical ENAs, which might not be incorporated into routine anti-ENA testing [108]. An example is detection of a nucleolar staining pattern, which is highly specific for scleroderma.

CONCLUSION

An occult connective tissue disease should be considered in every patient presenting with interstitial lung disease-related symptomatology. Connective tissue diseases that may mimic chronic idiopathic interstitial pneumonias include rheumatoid arthritis, polymyositis/dermatomyositis, scleroderma, Sjögren's syndrome, mixed connective tissue disease and undifferentiated connective tissue disease. A high index of suspicion is required for patients with lung biopsy results consistent with nonspecific interstitial pneumonia. In order to exclude a subclinical connective tissue disease, the clinical examination should be thorough and include a search for signs of systemic disease in various organs, including skin and vascular and musculoskeletal

system. In most cases, immunological testing is required to confirm the connective tissue disease diagnosis.

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