Evaluation of Lung Disease in Patients with Connective Tissue Disease

2

Aryeh Fischer and Kevin K. Brown

Introduction

The connective tissue diseases (CTDs) refer to the spectrum of systemic rheumatologic illnesses characterized by immune dysregulation with autoimmune phenomena (e.g., circulating autoantibodies) and immune-mediated organ dysfunction. In general, they include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis/dermatomyositis (including anti-synthetase syndrome), primary Sjögren's syndrome, mixed CTD (MCTD), and undifferentiated CTD. While these disorders are often considered as a group, there is significant clinical heterogeneity among them. Each can potentially impact all organ systems, with the lungs as a common target; and all patients with CTD are at risk for developing associated clinically significant lung disease [1, 2].

As reviewed in Chap. 7, there are a wide variety of pulmonary manifestations associated with the CTDs, with essentially every anatomic compartment of the respiratory tract at risk of injury [1–3]. Certain characterized diseases are more commonly associated with specific patterns of lung involvement (Table 2.1) [1]. As examples, in patients with SSc, pulmonary involvement is the leading cause of mortality and is typically manifested by interstitial lung disease (ILD) or pulmonary hypertension (PH). In contrast, in SLE, ILD and PH occur much less frequently—while pleural disease occurs quite commonly. Patients with rheumatoid arthritis (RA) and Sjögren's syndrome often develop airways disease (bronchiolitis and bronchiectasis) and ILD, whereas patients with poly-/dermatomyositis frequently develop ILD and yet rarely develop airway complications [1].

Depending upon the clinical context, CTD-associated lung disease varies by time of onset, pattern of lung involvement, and disease severity. Indeed, ILD may be the initial manifestation of a CTD (with extrathoracic features of the CTD developing months or even years later) [4–7] or may be identified in well-established, long-standing CTD [2]. Furthermore, abnormalities found on chest imaging or pulmonary physiology may be subclinical, asymptomatic and stable, or chronically progressive or may present in a fulminant, life-threatening manner.

In this chapter we discuss our approach to the evaluation of lung disease in the CTD patient. We focus specifically on the ILD evaluation because this lung manifestation occurs across the entire spectrum of CTD, is an area in which the importance of a multidisciplinary approach has been demonstrated, is potentially the most clinically

A. Fischer, M.D. (✉)
Division of Rheumatology, Department of Medicine, Autoimmune Lung Center, National Jewish Health, 1400 Jackson Street G07, Denver, CO 80206, USA
e-mail: fischera@njhealth.org

K.K. Brown, M.D.
Department of Medicine, National Jewish Health, 1400 Jackson Street, Denver, CO 80401, USA

P.F. Dellaripa et al. (eds.), *Pulmonary Manifestations of Rheumatic Disease: A Comprehensive Guide*,
DOI 10.1007/978-1-4939-0770-0_2,

Table 2.1 Most common CTD-associated pulmonary manifestations

	SSc	RA	Primary Sjögren's	MCTD	PM/DM	SLE
Airways	–	++	++	+	–	+
ILD	+++	++	++	++	+++	+
Pleural	–	++	+	+	–	+++
Vascular	+++	–	+	++	+	+
DAH	–	–	–	–	–	++

The number of + signs indicates relative prevalence of each manifestation
SSc systemic sclerosis, *RA* rheumatoid arthritis, *CTD* connective tissue disease, *MCTD* mixed connective tissue disease, *PM/DM* polymyositis/dermatomyositis, *SLE* systemic lupus erythematosus, *ILD* interstitial lung disease, *DAH* diffuse alveolar hemorrhage
Used with permission from Fischer A, du Bois RM. A Practical Approach to Connective Tissue Disease-Associated Lung Disease. In Baughman RP, duBois RM (eds): Diffuse Lung Disease: A Practical Approach. 2nd ed. New York: Springer; 2012

meaningful pulmonary manifestation, and often poses a significant diagnostic and management challenge for the practicing clinician.

The Pulmonary Evaluation by Clinical Context

Case Vignette 1

A 55-year-old man with well-established seropositive RA presents with recent-onset cough and dyspnea. He is a former smoker. The articular aspects of his RA are well controlled on chronic methotrexate, infliximab, and low-dose corticosteroids. His examination does not reveal synovitis. He has audible crackles in his lower lung zones bilaterally. He has a normal complete blood count and normal comprehensive metabolic panel. His erythrocyte sedimentation rate (ESR) is normal. He has a mild restrictive defect on pulmonary function testing and resting room-air pulse oximeter reading of 91 %. His high-resolution computed tomographic imaging shows evidence of a fibrotic interstitial pneumonia (Fig. 2.1).

Does this patient have CTD-ILD? How should we approach his evaluation?

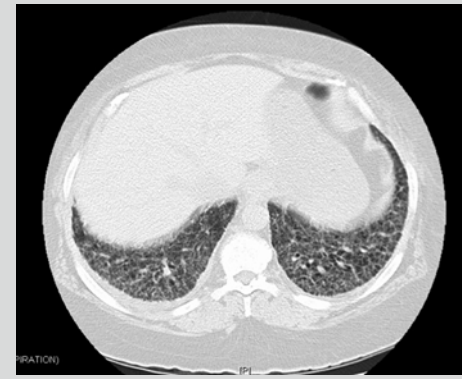

Fig. 2.1 High-resolution computed tomographic image in a patient with rheumatoid arthritis demonstrating evidence of a lower lobe-predominant fibrosing interstitial pneumonia

ILD in Established CTD

Chest imaging evidence of ILD is commonly identified in patients with an established, preexisting CTD. In fact, recent studies have shown radiographic prevalence rates of subclinical ILD of 33–57 % in various CTD cohorts [8]. ILD is particularly common in patients with SSc, PM/DM, RA, primary Sjögren's syndrome, and MCTD. However, just because a patient with CTD is identified to have parenchymal lung disease does not mean the two are necessarily related. For example, the presence of preexisting SSc may be

associated with the development of lung injury due to other causes (e.g., aspiration-associated pneumonitis). Furthermore, because CTD patients are often on immunosuppressive medications, the finding of new pulmonary infiltrates in these patients should raise suspicion of respiratory infection—with either typical or atypical pathogens—and medication-induced lung toxicity. As with any patient that presents with interstitial infiltrates, a comprehensive evaluation is needed to explore all potential etiologies (e.g., infection, medication toxicity, environmental and occupational exposures, familial disease, smoking-related lung disease, malignancy, etc.). The determination that the ILD is truly *associated* with the preexisting CTD requires a thorough process of elimination, and this evaluation is enhanced by a multidisciplinary approach [5, 9].

In general, when considering the evaluation of ILD in patients with CTD, we consider the steps discussed next.

Confirm the Presence of a CTD

This may be simple, especially when the background CTD is well characterized and established, such as with small joint synovitis and RF and CCP positive RA. Yet, quite often, the precise rheumatologic diagnosis is uncertain and the development of ILD may impact its classification. Take for instance the patient with an isolated positive SS-A autoantibody that may have been considered to have primary Sjögren's syndrome. If the patient evolves to a presentation of fulminant acute respiratory distress syndrome with lung injury patterns of nonspecific interstitial pneumonia (NSIP), diffuse alveolar damage, and overlapping organizing pneumonia (OP), along with radiographic features of esophageal dysmotility and the peripheral digital fissuring of "mechanic's hands," one might consider an anti-synthetase syndrome, rather than what was initially suspected—in the absence of lung disease—to be more likely a case of primary Sjögren's syndrome.

Determine Whether the ILD Pattern "Fits"

All of the well-characterized lung injury patterns as defined by high-resolution computerized tomographic (HRCT) scanning are known to occur across the spectrum of CTD [10], with some patterns occurring more commonly with specific CTD. For example, a NSIP pattern is the most frequent ILD pattern seen in the setting of SSc [11, 12], while the usual interstitial pneumonia (UIP) pattern appears to be more common in RA [13–15]. Overlapping patterns such as UIP and NSIP or NSIP and organizing pneumonia (OP) are not unusual and can be considered almost routine in disorders such as PM/DM. More unusual patterns such as lymphocytic interstitial pneumonia (LIP) with cystic lung disease (e.g., especially with Sjögren's) and primary airways disease (e.g., bronchiolitis) may also occur in specific settings.

Exclude Infection and Medication-Induced Pneumonitis

As emphasized, just because the patient has a CTD does not preclude the possibility of alternative etiologies for ILD. A comprehensive and multidisciplinary evaluation is needed in patients with CTD and ILD and rendering a diagnosis of CTD-*associated* ILD requires exclusion of other etiologies for the ILD. In particular pulmonary infection and drug-induced lung disease are almost always in the differential.

Perform Bronchoalveolar Lavage When Clinically Indicated to Exclude Infection

In CTD-ILD patients, bronchoalveolar lavage (BAL) can be useful in sorting through the initial differential diagnosis, especially to exclude infection. Its usefulness as a baseline predictor of disease progression however is unclear. Silver and colleagues have shown that BAL neutrophilia or eosinophilia in patients with SSc-ILD is useful as a predictor of progressive ILD [16, 17]. However, two recent well-designed prospective studies failed to demonstrate any prognostic significance obtained from BAL in patients with SSc-ILD [18, 19], and hence, the routine use of BAL to solely predict the likelihood of disease progression in CTD-ILD is not recommended.

Transbronchial biopsy is of limited value in the evaluation of parenchymal lung disease in CTD, but may be diagnostic in more airway-centric complications such as bronchiolitis or assessing for malignancy.

Biopsy the Atypical Scenario

Because data have yet to show that determining a specific histopathologic pattern of lung injury impacts prognosis in CTD-ILD, the role of surgical lung biopsy in patients with preexisting CTD remains controversial. The distinction between the specific ILD subtypes (e.g., UIP vs. NSIP) is known to have baseline prognostic significance among patients with idiopathic interstitial pneumonia (IIP)—but does not appear to be as prognostically significant in patients with CTD. In the largest series of biopsied SSc-ILD subjects ($n=80$), Bouros and colleagues showed that changes in diffusing capacity over time—but not baseline histopathologic pattern—predicted prognosis [11]. Similarly, in their cohort of 93 patients with a variety of CTD-ILD, Park and colleagues demonstrated that age, pulmonary function, and degree of dyspnea were of prognostic importance—but differences in pattern of lung injury did not impact survival [20]. The relatively small study cohort sizes and the impact of selection and referral bias cannot be discounted and therefore the predictive power of different patterns of lung histopathology remains uncertain in CTD-ILD. Furthermore, CTD-ILD patients tend to be treated with immunosuppressive therapies—targeting both progressive ILD and the extrathoracic inflammatory features—irrespective of specific ILD pattern. In this context, because the biopsy finding may not impact on treatment decisions, including immunosuppression, when the chest imaging pattern provides a strongly suggestive but not definitive pattern diagnosis that is consistent with what would be expected under the clinical conditions, clinicians often elect not to proceed with a surgical biopsy.

In general, we believe a surgical lung biopsy may be appropriate in patients with preexisting CTD in cases when there are clinically significant concerns for an alternative explanation for the underlying lung disease (e.g., hypersensitivity pneumonitis), when the chest imaging pattern on HRCT is atypical for underlying CTD, when the HRCT features suggest malignancy or infection (e.g., progressive nodules, cavitation, consolidation, pleural thickening, or effusion), or when a specific pattern cannot be identified by HRCT. Ultimately, the decision of whether to proceed with surgical lung biopsy is individualized, with due consideration for its associated risks, and whether its findings will impact on management and prognosis.

Case Vignette 2

A 40-year-old woman presents with acute onset of exertional fatigue, dyspnea, and cough. She has no relevant past medical history, takes no medications, and is a never smoker. Her review of systems is notable for recent development of arthralgias, digital edema, and Raynaud's phenomenon. On examination she has puffy hands without synovitis or sclerodactyly, a few scattered palmar telangiectasia, mild periungual erythema, and audible lower zone crackles bilaterally. Her laboratory studies note a positive antinuclear antibody (ANA) with a titer of 1:1,280 and nucleolar-staining pattern. She also has a positive anti-Scl-70 antibody. She has a normal set of pulmonary function tests. Her HRCT demonstrates suggestive features of the NSIP pattern of lung injury (Fig. 2.2).

Does this patient have CTD-ILD? How should we approach her evaluation?

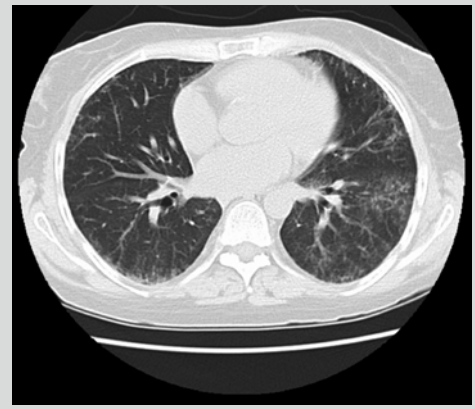

Fig. 2.2 High-resolution computed tomographic image in a patient presenting with an idiopathic interstitial pneumonia in a pattern suggestive of nonspecific interstitial pneumonia

ILD as the First Manifestation of a CTD

Considering the possibility of underlying CTD is an important aspect of the evaluation of patients presenting with an IIP. Within this scenario, the identification of occult CTD is common. A recent study reported that of 114 consecutive ILD patients evaluated at a tertiary referral center, 17 (15 %) were confirmed to have a new CTD diagnosis [21]. There is no standardized approach to the assessment of underlying CTD. Current practice includes performing a thorough history and physical examination and testing for circulating autoantibodies. Many centers have found that a multidisciplinary approach that includes rheumatologic consultation may also be useful. In practice, it is both unrealistic and impractical to have rheumatologic evaluation for all new cases of ILD, but certain proposed guidelines for deciding when to get rheumatologic consultation may be more realistic (Table 2.2) [5].

Table 2.2 Suggested categories of ILD patients that require further rheumatologic evaluation

1. Women, particularly those younger than 50
2. Any patient with extrathoracic manifestations highly suggestive of CTD
a. That is, Raynaud's phenomenon, esophageal hypomotility, inflammatory arthritis of the metacarpal-phalangeal joints or wrists, digital edema, or symptomatic keratoconjunctivitis sicca
3. All cases of NSIP, LIP, or any ILD pattern with secondary histopathology features that might suggest CTD
a. That is, extensive pleuritis, dense perivascular collagen, lymphoid aggregates with germinal center formation, prominent plasmacytic infiltration
4. Patients with a positive ANA or RF in high titer (generally considered to be ANA > 1:320 or RF > 60 IU/mL), a nucleolar-staining ANA at any titer, or any positive autoantibody specific as to a particular CTD
a. That is, anti-CCP, anti-Scl-70, anti-Ro, anti-La, anti-dsDNA, anti-Smith, anti-RNP, anti-tRNA synthetase

Used with permission from Fischer A, du Bois RM. A Practical Approach to Connective Tissue Disease-Associated Lung Disease. In Baughman RP, duBois RM (eds): Diffuse Lung Disease: A Practical Approach. 2nd ed. New York: Springer; 2012

Because the extrathoracic features of occult CTD can be subtle, confirming the presence of underlying CTD can be challenging. One such study evaluated whether ILD as the sole presentation of CTD can be differentiated from an IIP [22]. Sixty-eight patients that presented with an ILD were followed prospectively over 11 years. Thirteen (19 %) eventually developed a characterizable CTD. The prevalence of a positive rheumatoid factor (RF) or ANA was no different in the group that developed CTD compared with those that did not. The authors concluded that patients defined as having an IIP could not be distinguished from those that develop CTD-ILD before the systematic manifestations appear [22].

As the following select studies demonstrate, a thorough—and multidisciplinary—evaluation with heightened surveillance for subtle extrathoracic features of CTD, assessing a broader array of autoantibodies, and consideration of radiographic and histopathologic features make the detection of occult CTD more likely.

One small series from a multidisciplinary ILD program that incorporated rheumatologic evaluation described six patients evaluated within a 12-month span for presumed IIP [23]. All were found to have a positive nucleolar-pattern ANA, along with either an anti-Th/To or anti-Scl-70 antibody, and all had subtle extrathoracic features of SSc that included telangiectasia, Raynaud's phenomenon, digital edema, or esophageal hypomotility. This small series reinforced the concept that ILD may be the presenting manifestation of SSc, that engaging rheumatology for ILD evaluation can be helpful, and that suspicions for SSc are warranted in patients with a nucleolar-pattern ANA and NSIP or UIP [23, 24]. Another study from a multidisciplinary ILD program described a retrospectively evaluated cohort of 114 consecutive patients [21]. Thirty-four subjects (30 %) were found to have CTD-ILD and of these, only half had presented with a preexisting CTD. These authors argued that when confronted with an IIP, the presence of younger age, high-titer ANA, and elevated muscle enzymes were associated with underlying CTD. In another study, a cohort

of 50 ILD patients referred to a tertiary referral center were retrospectively assessed and described [25]. Of the 25 patients confirmed to have a diagnosis of CTD-ILD—only after multidisciplinary evaluation—28 % had been initially referred with a diagnosis of IPF!

Another recent study highlights the importance of maintaining a heightened suspicion for underlying CTD in cases of NSIP—even when the ANA and RF are negative [6]. Nine patients evaluated over a 2-year period with idiopathic NSIP were ANA and RF negative but found to have the anti-synthetase syndrome based on the presence of a tRNA synthetase antibody (PL-7 or PL-12), NSIP, and subtle extrathoracic features that included "mechanic's hands," Raynaud's phenomenon, inflammatory arthritis, myositis, or esophageal hypomotility [6]. In another study, 198 consecutive cases of IIP were screened with a panel of anti-tRNA synthetase antibodies and identified positive anti-synthetase antibodies in 13 cases (7 %) [26]. They reported that those with positive antibodies were younger and more likely to have NSIP or UIP with lymphoid follicules. Furthermore, among the 13 with a positive tRNA synthetase antibody, extrathoracic manifestations of anti-synthetase syndrome were retrospectively identified in 7 cases [26].

Taken together, there are many variables to consider when evaluating a patient with presumed IIP for the presence of occult CTD. We have found that careful attention to the following items is often helpful.

Clinical Features

Demographic features can help distinguish the patient with an underlying CTD. In comparison to IPF, patients with CTD-ILD are more likely to be younger and female. A detailed review of systems and thorough physical examination is useful. Certain specific clinical features lend more support for underlying CTD than others. Of the CTD symptoms encountered in patients with IIP, perhaps none is as important as Raynaud's phenomenon. The presence of Raynaud's phenomenon is associated with a pattern of NSIP and when identified in a patient with ILD should raise strong suspicions for underlying CTD in general and SSc (with or without overt skin thickening) in particular. Indeed, Raynaud's phenomenon is encountered in nearly all patients with SSc and is a common finding in patients with PM/DM, anti-synthetase syndrome, primary Sjögren's syndrome, MCTD, SLE, and UCTD. Performing nailfold capillary microscopy is useful when assessing a patient with Raynaud's phenomenon. In particular, the presence of dilated or tortuous capillary loops or significant areas lacking capillary loops (i.e., capillary dropout) may be suggestive of SSc or PM/DM (Fig. 2.3).

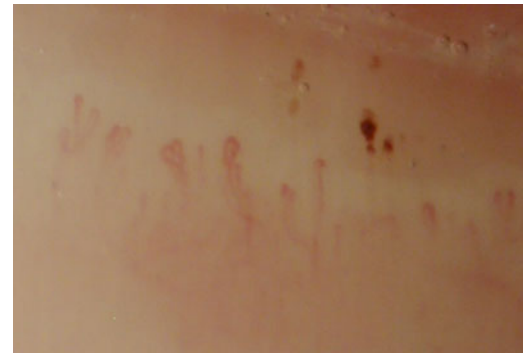

Fig. 2.3 A nailfold capillary microscopic image from a patient with systemic sclerosis. Note the presence of marked capillary loop tortuosity, dilation, and areas of vascular dropout. (Used with permission from Fischer A, du Bois RM. A Practical Approach to Connective Tissue Disease-Associated Lung Disease. In Baughman RP, duBois RM (eds): Diffuse Lung Disease: A Practical Approach. 2nd ed. New York: Springer; 2012)

The reporting of symmetric joint swelling or stiffness, or identifying synovitis on physical examination, is very useful. Because inflammatory arthritis is encountered in all of the CTDs, autoantibody profiles may be needed to clarify which specific CTD is present. In contrast, symptoms such as gastroesophageal reflux, pain, fatigue, dry eyes, dry mouth, alopecia, and weight loss are not nearly as helpful because they are ubiquitous and not nearly as specific for CTD.

The cutaneous manifestations of SSc and anti-synthetase syndrome are worthy of special mention because these two disorders are so commonly associated with ILD and their extrathoracic features are very specific and yet often quite subtle. It is important to recognize that the "mechanic's hands" sign of anti-synthetase syndrome can be

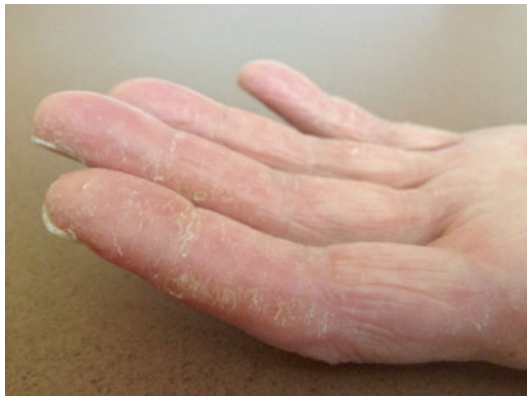

Fig. 2.4 A photograph of the distal digital fissuring characteristic of "mechanic's hands" in a patient with the anti-synthetase syndrome

as subtle as only mild distal digital fissuring (Fig. 2.4) and that palmar telangiectasia may be limited to the finding of only few scattered dilated capillaries. Nonetheless, when such findings are present in a patient with an IIP, they are highly suggestive of underlying CTD.

Circulating Autoantibodies

Autoantibody assessment is an important part of the evaluation of patients with IIP. For patients with ILD in whom there is clinical suspicion of an underlying CTD, we recommend a broad panel of autoantibodies as a screening test (Table 2.3). It is also important to take note of the pattern of immunofluorescence when the ANA is positive, as the nucleolar-staining ANA pattern in patients with ILD may suggest SSc spectrum of disease [23, 24, 27].

Importantly, we highlight that the ANA and RF are relatively poor screening tests: they have low specificity—particularly when present at low titer—and can be seen in healthy individuals. In addition, given that a negative ANA and RF may dissuade some clinicians from pursuing further evaluation, cases of occult CTD that may be ANA and RF negative (e.g., anti-synthetase syndrome) are missed.

Chest Imaging Features

Thoracic HRCT imaging plays a central role in the evaluation of ILD by providing detailed information on the pattern, distribution and extent of the ILD, and the presence of extraparenchymal abnormalities including pleural disease and pericardial and esophageal features. In contrast to IIP, patients with CTD-ILD are more likely to have pleural effusions, pericardial effusions, pericardial thickening, and esophageal dilatation [28]. Patients with CTD are also more likely to have an HRCT pattern suggestive of NSIP when compared to patients without CTD [28]. HRCT has varying degrees of correlation with histopathologic pattern. Among CTD-ILD patients with a typical HRCT pattern for UIP, the histopathology almost always correlates [28–30]. Interestingly, the converse does not hold true; CTD patients with histopathologic patterns of UIP may have HRCT patterns suggestive of NSIP [28–30]. As discussed previously, noting atypical patterns of lung injury may impact decisions to perform surgical lung biopsy.

Table 2.3 Useful antibodies for CTD-ILD assessment

Autoantibody	Commonly associated CTD
High-titer ANA (≥1:320 titer)	Many
High-titer RF (≥60 IU/mL)	RA, Sjögren's syndrome, SLE
Anti-CCP	RA
Anti-centromere	Systemic sclerosis
Anti-nucleolar-ANA	Systemic sclerosis
Anti-Ro (SS-A)	Many
Anti-La (SS-B)	SLE, Sjögren's syndrome
Anti-Smith	SLE
Anti-ribonucleoprotein	SLE, MCTD
Anti-dsDNA	SLE
Anti-topoisomerase (Scl-70)	Systemic sclerosis
Anti-tRNA synthetase antibodies	Poly-/dermatomyositis (anti-synthetase syndrome)
Anti-PM-Scl	Systemic sclerosis/myositis overlap
Anti-Th/To	Systemic sclerosis
Anti-U3 ribonucleoprotein	Systemic sclerosis
Anti-MDA-5 (CADM)	Clinical amyopathic dermatomyositis

Used with permission from Fischer A, du Bois RM. A Practical Approach to Connective Tissue Disease-Associated Lung Disease. In Baughman RP, duBois RM (eds): Diffuse Lung Disease: A Practical Approach. 2nd ed. New York: Springer; 2012

Histopathologic Features

Several histopathologic features may be useful when trying to distinguish an IIP from CTD-ILD. An initial clue to an underlying CTD is the presence of multi-compartment involvement on the biopsy; in addition to parenchymal lung injury, there may be components of airways, vascular, or pleural disease [31, 32]. When compared to IPF, CTD-UIP is characterized by fewer fibroblastic foci, less overall fibrosis, and less honeycombing [33, 34]. Flaherty and colleagues compared the histopathologic features of 9 patients with CTD-UIP to that of 99 patients with IPF [34]. Those with CTD-UIP were younger, had better lung function, and shorter duration of symptoms. They found that those with IPF had significantly higher fibroblast focus scores than CTD-UIP and that the fibroblast focus score was the most discriminative feature between these groups [34]. Song and colleagues compared histopathologic features in 39 patients with CTD-UIP to 61 patients with IPF [33]. They found that the biopsies in those with CTD-UIP had fewer fibroblast foci and less honeycombing but had more germinal center formation and more evidence of inflammation than seen with IPF.

Additional histopathologic features that lend support for the presence of underlying CTD include the presence of lymphoid aggregates, germinal centers, increased perivascular collagen, follicular bronchiolitis, lymphoplasmacytic inflammation, eosinophil infiltration, or pleuritis [31, 32].

Determining Severity of Impairment

A standardized assessment for disease progression is important for the longitudinal monitoring of patients with CTD-ILD and helps guide therapeutic decision-making regarding the initiation, modification, or cessation of therapy. A number of objective modalities commonly employed for disease monitoring are detailed in this section.

Dyspnea and Quality of Life Measures

The use of a reproducible, subjective indicator of a patient's level of breathlessness, exercise capacity, and quality of life can provide clinically important data. By using a standardized and validated clinical tool to evaluate dyspnea, the clinician may assess respiratory disease progression and functionality over time. A number of dyspnea indices have been validated in respiratory disease and the choice of which index to use is less important than their consistent implementation by practitioners to reliably quantify subjective dyspnea. In one study, the self-reported measures of the Multi-Dimensional Health Assessment Questionnaire, University of California San Diego Dyspnea Questionnaire, and Dyspnea-12 Questionnaire were found to be useful in the assessment of patients with a wide spectrum of CTD-ILD [35]. These measures yielded meaningful information beyond that provided by pulmonary physiology and confirmed that dyspnea is strongly associated with perceived day-to-day functioning and global well-being in CTD-ILD.

Pulmonary Function Testing

Serial assessment of the forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) allows for objective quantification of ventilatory capacity and gas exchange, respectively. These parameters are useful in assessing the degree of respiratory impairment due to ILD and may provide clues about the presence of coexistent PH as well. They are especially helpful when trying to assess for disease progression and response to therapy. Changes in FVC, and to a lesser degree of confidence in DLCO, over time predict survival in IPF and, therefore, are commonly used as surrogate markers for response to therapy in ILD in general [36]. Patients who decline $\geq$10 % of predicted FVC or $\geq$15 % of DLCO are considered to have clear and clinically significant evidence of progressive disease. In patients with CTD-ILD, pulmonary physiology appears to be a stronger predictor of survival than underlying histopathologic pattern seen at the time of diagnosis [11, 20].

Six-Minute Walk Test

The 6-minute walk test (6MWT) objectively assesses for ILD severity, disease progression, and response to therapy [37–39]. In a multicenter treatment trial in which the 6MWT was specifically evaluated in SSc-ILD, the investigators found that although the distance walked was reproducible, it correlated only weakly with FVC and Borg dyspnea index, suggesting that these tests measure different facets of disease progression [39]. Furthermore, because of significant extrathoracic variables—and musculoskeletal impairment in particular—the use of 6MWT as an end point for clinical trials in CTD-ILD has been disputed. In clinical practice, however, we find the 6MWT to be a generally useful test to perform longitudinally. It is relatively inexpensive, easy to perform, and provides an additional objective measure of exercise capacity for which to help plot the longitudinal clinical course of a patient.

Thoracic High-Resolution Computed Tomography

As discussed previously, HRCT imaging yields valuable information about ILD including the pattern and extent of disease, an assessment of disease progression, and the evaluation of extraparenchymal abnormalities. In many cases of CTD-ILD, a specific radiologic pattern (e.g., UIP or NSIP) can be determined with a high degree of confidence. This pattern recognition within specific clinical scenarios may obviate the need for surgical lung biopsy and provide prognostic information. The presence of a fibrotic radiographic pattern as evidenced by reticular opacities, traction bronchiectasis, and honeycombing is predictive of poor outcomes in both IIP and RA-ILD [13, 29, 40, 41]. A recent study of 215 subjects with SSc-ILD demonstrated that the HRCT extent of fibrosis and degree of FVC reduction provide discriminatory prognostic information [42]. The authors proposed a subclassification of SSc-ILD as "limited" or "extensive" based upon the estimation of extent of fibrosis on HRCT and impairment in FVC. This simple staging system provided a more accurate prognostic separation than has been achieved with any single index in isolation [42].

Management Considerations

It is important to recognize that not all patients with CTD-ILD require pharmacologic treatment (see Chap. 14). Radiographic findings of ILD on HRCT are common, but only a subset of patients will show clinically significant, progressive disease. The decision to treat CTD-ILD often rests upon whether the patient is clinically impaired by their lung disease, whether it is progressive, and what comorbid conditions or mitigating factors exist [43]. Therapy for CTD-ILD is generally reserved for those patients with clinically significant, progressive disease, and this determination is based upon a constellation of clinical assessment tools that include both subjective and objective measures of respiratory impairment [43].

The evaluation and management of patients with CTD-ILD is optimized by effective multidisciplinary interactions among pulmonologists and rheumatologists. In particular, when considering immunomodulatory therapy options for CTD-ILD, both intrathoracic and extrathoracic disease manifestations and degrees of activity need to be assessed and taken into consideration when designing a therapeutic regimen. Given the heterogeneity in disease presentation, the multiple systems that may be affected, and the broad range of disease severity, coordinated care is essential. In all cases of CTD-ILD, disease monitoring, choice of therapy, and ongoing longitudinal assessment and reassessment of a treatment response are complex and are optimized by effective collaborative care among pulmonologists, rheumatologists, and other health-care providers.

Summary

Lung disease is a common manifestation of CTD and is associated with significant morbidity and mortality. The evaluation of lung disease, and ILD in particular, in patients with CTD is complex

because of the heterogeneity of the CTDs and the varied types and degrees of severity of ILD encountered and because ILD can be identified at any point in time in these patients. A thorough—and multidisciplinary—evaluation is needed when CTD patients develop ILD or when evaluating ILD patients for the presence of occult CTD. Determining that ILD is associated with an established CTD requires the exclusion of alternative etiologies and thorough assessments of the clinical features of both the CTD and ILD. The detection of occult CTD in patients with so-called "idiopathic" ILD requires careful attention to the demographic profile, historical clues, subtle physical examination findings, specific autoantibody positivity, and radiologic and histopathologic features and can be optimized by a multidisciplinary approach that includes rheumatologic collaboration. A standardized assessment with the serial implementation of objective tests to determine disease severity and evidence of progression is important for the longitudinal monitoring of patients with CTD-ILD and helps guide management considerations.

References

1. Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders. Lancet. 2012;380:689–98.
2. Frankel SK, Brown KK. Collagen vascular diseases of the lung. Clin Pulm Med. 2006;13:25–36.
3. Olson AL, Brown KK. Connective tissue disease-associated lung disorders. Eur Respir Mon. 2009; 46:225–50.
4. Cottin V. Interstitial lung disease: are we missing formes frustes of connective tissue disease? Eur Respir J. 2006;28:893–6.
5. Fischer A, du Bois RM. A practical approach to connective tissue disease-associated lung disease. In: Baughman RP, du Bois RM, editors. Diffuse lung disease: a practical approach. 2nd ed. New York: Springer; 2012.
6. Fischer A, Swigris JJ, du Bois RM, et al. Anti-synthetase syndrome in ANA and anti-Jo-1 negative patients presenting with idiopathic interstitial pneumonia. Respir Med. 2009;103:1719–24.
7. Fischer A, West SG, Swigris JJ, Brown KK, du Bois RM. Connective tissue disease-associated interstitial lung disease: a call for clarification. Chest. 2010; 138:251–6.
8. Doyle TJ, Hunninghake GM, Rosas IO. Subclinical interstitial lung disease: why you should care. Am J Respir Crit Care Med. 2012;185:1147–53.
9. Fischer A. Interstitial lung disease: a rheumatologist's perspective. J Clin Rheumatol. 2009;15:95–9.
10. ATS/ERS. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med. 2002;165:277–304.
11. Bouros D, Wells AU, Nicholson AG, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med. 2002; 165:1581–6.
12. Kim DS, Yoo B, Lee JS, et al. The major histopathologic pattern of pulmonary fibrosis in scleroderma is nonspecific interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis. 2002;19:121–7.
13. Kim EJ, Collard HR, King Jr TE. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. Chest. 2009;136:1397–405.
14. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2010; 35: 1322–8.
15. Lee HK, Kim DS, Yoo B, et al. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest. 2005; 127: 2019–27.
16. Kowal-Bielecka O, Kowal K, Highland KB, Silver RM. Bronchoalveolar lavage fluid in scleroderma interstitial lung disease: technical aspects and clinical correlations: review of the literature. Semin Arthritis Rheum. 2012;40:73–88.
17. Silver RM, Miller KS, Kinsella MB, Smith EA, Schabel SI. Evaluation and management of scleroderma lung disease using bronchoalveolar lavage. Am J Med. 1990;88:470–6.
18. Goh NS, Veeraraghavan S, Desai SR, et al. Bronchoalveolar lavage cellular profiles in patients with systemic sclerosis-associated interstitial lung disease are not predictive of disease progression. Arthritis Rheum. 2007;56:2005–12.
19. Strange C, Bolster MB, Roth MD, et al. Bronchoalveolar lavage and response to cyclophosphamide in scleroderma interstitial lung disease. Am J Respir Crit Care Med. 2008;177:91–8.
20. Park JH, Kim DS, Park IN, et al. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. Am J Respir Crit Care Med. 2007;175:705–11.
21. Mittoo S, Gelber AC, Christopher-Stine L, Horton MR, Lechtzin N, Danoff SK. Ascertainment of

collagen vascular disease in patients presenting with interstitial lung disease. Respir Med. 2009;103:1152–8.
22. Homma Y, Ohtsuka Y, Tanimura K, et al. Can interstitial pneumonia as the sole presentation of collagen vascular diseases be differentiated from idiopathic interstitial pneumonia? Respiration. 1995;62:248–51.
23. Fischer A, Meehan RT, Feghali-Bostwick CA, West SG, Brown KK. Unique characteristics of systemic sclerosis sine scleroderma-associated interstitial lung disease. Chest. 2006;130:976–81.
24. Fischer A, Pfalzgraf FJ, Feghali-Bostwick CA, et al. Anti-th/to-positivity in a cohort of patients with idiopathic pulmonary fibrosis. J Rheumatol. 2006;33: 1600–5.
25. Castelino FV, Goldberg H, Dellaripa PF. The impact of rheumatological evaluation in the management of patients with interstitial lung disease. Rheumatology (Oxford). 2011;50:489–93.
26. Watanabe K, Handa T, Tanizawa K, et al. Detection of antisynthetase syndrome in patients with idiopathic interstitial pneumonias. Respir Med. 2011;105:1238–47.
27. Steen VD. Autoantibodies in systemic sclerosis. Semin Arthritis Rheum. 2005;35:35–42.
28. Hwang JH, Misumi S, Sahin H, Brown KK, Newell JD, Lynch DA. Computed tomographic features of idiopathic fibrosing interstitial pneumonia: comparison with pulmonary fibrosis related to collagen vascular disease. J Comput Assist Tomogr. 2009;33: 410–5.
29. Lynch DA. Quantitative CT of fibrotic interstitial lung disease. Chest. 2007;131:643–4.
30. Lynch DA, Travis WD, Muller NL, et al. Idiopathic interstitial pneumonias: CT features. Radiology. 2005;236:10–21.
31. Fukuoka JLK. Practical pulmonary pathology. A diagnostic approach. 1st ed. Philadelphia: Churchill-Livingstone; 2005.
32. Leslie KO, Trahan S, Gruden J. Pulmonary pathology of the rheumatic diseases. Semin Respir Crit Care Med. 2007;28:369–78.
33. Song JW, Do KH, Kim MY, Jang SJ, Colby TV, Kim DS. Pathologic and radiologic differences between idiopathic and collagen vascular disease-related usual interstitial pneumonia. Chest. 2009; 136:23–30.
34. Flaherty KR, Colby TV, Travis WD, et al. Fibroblastic foci in usual interstitial pneumonia: idiopathic versus collagen vascular disease. Am J Respir Crit Care Med. 2003;167:1410–5.
35. Swigris JJ, Yorke J, Sprunger DB, et al. Assessing dyspnea and its impact on patients with connective tissue disease-related interstitial lung disease. Respir Med. 2010;104:1350–5.
36. du Bois RM, Weycker D, Albera C, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med. 2011; 184:1382–9.
37. Buch MH, Denton CP, Furst DE, et al. Submaximal exercise testing in the assessment of interstitial lung disease secondary to systemic sclerosis: reproducibility and correlations of the 6-min walk test. Ann Rheum Dis. 2007;66:169–73.
38. Eaton T, Young P, Milne D, Wells AU. Six-minute walk, maximal exercise tests: reproducibility in fibrotic interstitial pneumonia. Am J Respir Crit Care Med. 2005;171:1150–7.
39. Hallstrand TS, Boitano LJ, Johnson WC, Spada CA, Hayes JG, Raghu G. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. Eur Respir J. 2005;25:96–103.
40. Flaherty KR, Mumford JA, Murray S, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2003;168:543–8.
41. Kocheril SV, Appleton BE, Somers EC, et al. Comparison of disease progression and mortality of connective tissue disease-related interstitial lung disease and idiopathic interstitial pneumonia. Arthritis Rheum. 2005;53:549–57.
42. Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med. 2008;177: 1248–54.
43. Fischer A, Brown KK, Frankel SK. Treatment of connective tissue disease related interstitial lung disease. Clin Pulm Med. 2009;16:74–80.

http://www.springer.com/978-1-4939-0769-4

Pulmonary Manifestations of Rheumatic Disease
A Comprehensive Guide
Dellaripa, P.F.; Fischer, A.; Flaherty, K.R. (Eds.)
2014, XII, 222 p. 64 illus., 26 illus. in color., Hardcover
ISBN: 978-1-4939-0769-4