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INTERSTITIAL LUNG DISEASE (G TINO, SECTION EDITOR)

Connective tissue disease-associated interstitial lung disease: a review

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Abstract Interstitial lung disease (ILD) is commonly encountered in patients with connective tissue diseases (CTD). Besides the lung parenchyma, the airways, pulmonary vasculature and structures of the chest wall may all be involved, depending on the type of CTD. As a result of this so-called multi-compartment involvement, airflow limitation, pulmonary hypertension, vasculitis and extrapulmonary restriction can occur alongside fibro-inflammatory parenchymal abnormalities in CTD. Rheumatoid arthritis (RA), systemic sclerosis (SSc), *polymyositis/dermatomyositis* (PM/DM), Sjögren's syndrome (SjS), systemic lupus erythematosus (SLE), and undifferentiated connective tissue disease (UCTD), as well as mixed connective tissue disease (MCTD), can all be associated with the development of ILD. Nonspecific interstitial pneumonia (NSIP) is the most commonly observed histopathological pattern in CTD-ILD, but other patterns, including usual interstitial pneumonia (UIP), organizing pneumonia (OP), diffuse alveolar damage (DAD) and lymphocytic interstitial pneumonia (LIP), may occur. Although the majority of patients with CTD-ILD experience stable or slowly advancing ILD, a small yet significant group exhibits a more severe and progressive course. Randomized placebo-controlled trials evaluating the efficacy of immunomodulatory treatments have been conducted only in SSc-associated ILD. However, clinical experience suggests that a handful of immunosuppressive medications are potentially effective in a sizeable portion of patients with ILD caused by other CTDs. In this manuscript, we review the clinical characteristics and management of the most common CTD-ILDs.

Keywords Connective tissue disease · Interstitial lung disease · Autoimmune disease · Pulmonary fibrosis · Rheumatoid arthritis · Dermatomyositis · Polymyositis · Sjogren's syndrome · Progressive systemic sclerosis · Systemic lupus erythematosus · Mixed connective tissue disease · Undifferentiated connective tissue disease · Lung-dominant connective tissue disease

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Introduction

Lung involvement is common in connective tissue diseases (CTDs) and can lead to significant morbidity and shortened survival. Depending on the underlying CTD, various thoracic compartments can be involved simultaneously; although, for this review, we will focus on the parenchymal changes of CTD-associated interstitial lung disease (CTD-ILD). Most CTD-ILD presents with a dry cough, gradually progressive dyspnea and a restrictive ventilatory defect on pulmonary function tests (PFTs). Many patients diagnosed with CTD-ILD have a classifiable CTD at the time ILD is recognized; however, in up to 25 % of cases, a constellation of clinical and serological findings suggest, but are not entirely diagnostic of, a classifiable CTD. Patients in such a scenario have been labeled with "undifferentiated" CTD (UCTD), lung-dominant CTD and autoimmune-featured ILD by various investigators [1••, 2]. Lung disease can also predate extrapulmonary CTD manifestations by several years, thus making the distinction between CTD-ILD and an idiopathic interstitial pneumonia (IIP) difficult [3]. Below, we provide a general description of the physiological, histological and radiological findings and management features of CTD-ILD and proceed to highlight some of the unique and important aspects of ILD in the context of each individual CTD.

Clinical features of CTD-ILD

Pulmonary function testing (PFT) The classic PFT pattern observed in CTD-ILD is a restrictive ventilatory defect and reduced diffusion capacity (DLco). However, when other thoracic compartments such as airways, vasculature or chest wall are involved (as may occur in CTD), clinicians should be aware that a different constellation of PFT-abnormalities can arise. For example, a disproportionate reduction in DLco may signify ILD with coexistent emphysema or pulmonary hypertension [4••], or a significant reduction in lung volumes with relatively preserved DLco should raise suspicion for extrapulmonary restriction (e.g., chest wall skin thickening, respiratory muscle weakness or kyphoscoliosis).

Histopathological patterns Except for rheumatoid arthritis (RA), in which usual interstitial pneumonia (UIP)-pattern pathology is more common, the nonspecific interstitial pneumonia (NSIP) pattern of lung injury is most common across all CTD-ILD [5, 6•] Compared with cases in which UIP-pattern injury is idiopathic (i.e., idiopathic pulmonary fibrosis [IPF]), CTD-associated UIP (CTD-UIP) has fewer fibroblastic foci, smaller honeycomb cysts, a greater number of germinal centers and more inflammation [7]. Although results are conflicting, some studies suggest patients with CTD-UIP have a better prognosis than IPF-patients. Also a matter of debate, some studies suggest no difference in prognosis between CTD-UIP and CTD-NSIP, contrasting with what is known about the difference in prognosis between idiopathic NSIP and IPF [6•, 8, 9] Less commonly encountered injury patterns of CTD-ILD include organizing pneumonia (OP)—although OP not uncommonly occurs as a secondary feature in patients with CTD—diffuse alveolar damage (DAD), lymphocytic interstitial pneumonia (LIP) and desquamative interstitial pneumonia (DIP).

Because of conflicting study results, many clinicians are uncertain about the utility of surgical lung biopsy (SLBx) in their patients with CTD-ILD. On the one hand, many clinicians believe that, among patients with CTD-ILD, UIP-pattern histology confers a worse prognosis than NSIP-pattern histology. Those in this camp would have their CTD-ILD patients undergo SLBx, because the results could better define disease trajectory. On the other hand, clinicians not using SLBx in their patients with CTD-ILD are either unconvinced that the histological pattern trumps pulmonary physiology in determining prognosis, or more likely, do not expect the results to change management: they plan to treat (or perhaps already are treating) with immunosuppressive medications, and the SLBx pattern would not affect their choice of therapeutic agent or anticipated duration of therapy. When an etiology for the ILD other than CTD (e.g. hypersensitivity pneumonitis) is seriously considered, or when imaging features suggest malignancy or infection (e.g. progressive nodules, cavitation, consolidation, pleural thickening or effusion), there is greater consensus about the utility of SLBx in this patient population.

High-resolution computer tomography (HRCT) findings Most parenchymal abnormalities in CTD-ILD are easily appreciated with HRCT and commonly described using terminology applied to IIPs (Figs. 1 and 2). While each CTD demonstrates a predilection for a certain pattern of parenchymal involvement, significant overlap exists (Table 1) [10••, 11]. Overall, a radiographic NSIP-pattern is found most commonly in CTD-ILDs, and is characterized by intralobular and interlobular reticular opacities in a predominantly subpleural and basilar distribution. Ground-glass opacities are usually considered to represent a higher degree of cellularity and suggest the disease is potentially more responsive to treatment, although in some cases this is not true. Subpleural sparing—an opacity-free, thin rim of parenchyma directly adjacent to the pleura in the posterior zones of the lung bases—hints at an underlying NSIP-pattern of lung injury and argues against the UIP-pattern. Reticulation, traction bronchiectasis and honeycombing reflect fibrotic changes and more advanced ILD. Abnormalities in other thoracic structures (e.g., esophageal or pulmonary artery dilatation)—hinting at the presence of multi-compartment involvement—should raise suspicion for the presence of a CTD [12••, 13••].

Serological studies Serum auto-antibodies will be explored in the sections covering each of the CTDs below [13••].

General strategies in the management of CTD-ILD Not every patient with CTD-ILD requires treatment; thus, it is important to distinguish trivial disease (with low likelihood for progression) from clinically significant ILD. HRCT and PFTs are most helpful in objectively determining disease severity and its course over time, but strong consensus regarding which patients to treat, when and for how long has not been achieved for CTD-ILD. In our experience, patients with disease extent <10 % on HRCT and/or forced vital capacity

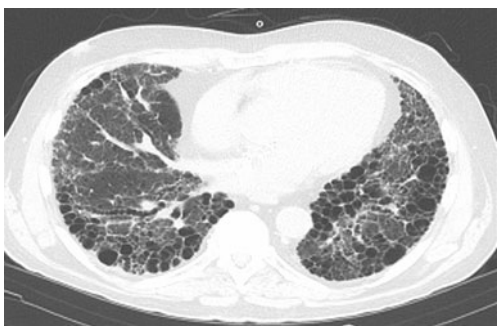

Fig. 1 Slice from a HRCT scan from a 65-year-old man with rheumatoid arthritis. Note the honeycombing characteristic of a radiographic UIP-pattern

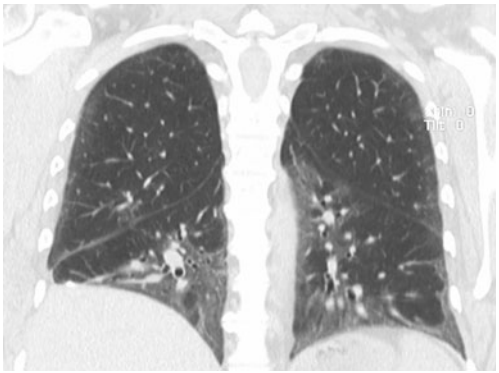

Fig. 2 Coronal view slice from a HRCT scan from a 58-year-old woman with dermatomyositis. Notice the ground-glass opacities and traction bronchiolectasis characteristic of mixed cellular and fibrotic NSIP

(FVC)>75 % and/or DLco>65 %, in the absence of respiratory symptoms, can be carefully monitored every 3–6 months for evidence of progression. Since immunomodulatory medications are associated with significant adverse effects, we reserve treatment for those cases with severe, extensive or progressive disease. Various regimens have been used to treat CTD-ILD, but the only large-scale, randomized trials have been conducted to examine the effectiveness of cyclophosphamide (or cyclophosphamide followed by azathioprine) in patients with SSc-ILD [14, 15]. Data for other immunomodulatory drugs (including azathioprine, mycophenolate mofetil and tacrolimus) stem from case reports and observational case series [16-18]. We typically evaluate the response to therapy every three months. A favorable response may be defined as improvement in symptoms and functional capacity, or disease extent on HRCT or pulmonary physiology; however, in this challenging spectrum of diseases, halting progression and maintaining stability should also be considered a success. As mentioned above, there are a number of questions that remain unanswered about the treatment of CTD-ILD, so this is an area ripe for investigation.

Table 1 Radiological pattern in CTD-ILD [10, 11]

	NSIP	UIP	OP	PH	DAD	LIP	Hemorrhage	Airways disease
RA	+	++++	++	+	+	+		++++
SSc	++++	+	+	+++	+			
PM/DM	++++	+	++++		+			
SjS	++	+	+	+	+	++++		+++
MCTD	++	+	+	+	+			
SLE	++	+	+	+	++	+	++	+

The number of '+' signs indicates the frequency of observed injury pattern, i.e., ++++ = very common or clinically prominent manifestation, + = less common, empty cells = rare or not described in this disease; RA=rheumatoid arthritis; SSc=systemic sclerosis; PM/DM=polymyositis/dermatomyositis; SjS=Sjögren's syndrome; MCTD=mixed-connective tissue disease; SLE=systemic lupus erythematosus

ILD in specific CTDs

Rheumatoid arthritis (RA) RA is the most common CTD and is characterized by an erosive inflammatory polyarthropathy with symmetrical arthritis and a range of pulmonary manifestations. While RA occurs more commonly in females (female to male ratio 3:1), RA-ILD is more frequent in males. The prevalence of RA-ILD varies from 5–58 %, depending on the case definition for ILD [19-21]. Smoking is a risk factor for RA-ILD, and emerging data suggest that cigarette smoke exerts its effects by promoting the citrullination of various proteins in the lung. In fact, theories have arisen that seropositive RA "starts" in the lung [22, 23]. Severe ILD may occur when joint disease is mild or well controlled with therapy—there appears to be no reliable correlation between the extent or severity of the joint disease and the development or progression of ILD in patients with RA.

RA-ILD manifests most commonly in the UIP-pattern, and less commonly with NSIP-pattern injury. However, clinicians caring for patients with RA must keep in mind that medications used to treat extrapulmonary disease (e.g., methotrexate) can cause ILD and predispose to opportunistic infections. Thus, a detailed drug history is crucial in all patients with CTD-ILD. A temporal relationship between drug initiation and symptom onset and then improvement after withdrawal can point toward drug-induced lung disease. However, delayed reactions or continued progression despite stopping the medication can occur, making the differentiation between drug-induced ILD and worsening RA-ILD challenging. In this situation, diagnostic BAL can help to exclude infectious etiologies, while BAL-lymphocytosis and/or eosinophilia with or without peripheral blood eosinophilia can further support the diagnosis of drug-induced ILD. Some of the most commonly prescribed medications implicated in pulmonary toxicity include methotrexate, leflunomide, gold salts, sulfasalazine, and anti-tumor necrosis factor (anti-TNF) antibodies [24-28] A helpful online tool listing all medications associated with pulmonary toxicity in further detail can be found at pneumotox.com [29••]. We advocate against the use of drugs with high rates of pulmonary toxicity in RA patients with pre-existing lung disease.

Due to the absence of randomized controlled trials, the treatment of RA-ILD remains entirely empirical. High-dose corticosteroids are often used in patients with potentially reversible patterns such as OP or those with flares of RA-ILD. In addition, cyclophosphamide, azathioprine, cyclosporine or mycophenolate have been used as steroid sparing agents or in steroid-refractory cases [17, 18, 30-32]. In our experience, biologic agents control the joint disease very well, but have minimal effect on ILD. Lung transplantation is offered by certain centers to RA-ILD patients with limited joint disease and relatively preserved functional status.

Systemic sclerosis Systemic sclerosis is the CTD with the largest percentage of patients afflicted with ILD (40–80 %, depending on method of ascertainment). Along with pulmonary hypertension (PH), ILD is a major cause of death in this disease [33•, 34]. The frequency of ILD depends on ethnicity, autoantibody pattern, and less so on the extent of skin disease. Most patients with SSc have high titers of antinuclear antibodies (ANA)—most often in a nucleolar pattern. Three antibodies with the highest specificity for SSc include antibodies against anti-RNA polymerase III (Pol3), anticentromere antibodies (ACA) and antibodies against topoisomerase (anti-Scl70). Anti-Scl70 antibodies are strongly associated with ILD [36]. Although ACA are protective from significant ILD, patients with ACA carry a high risk for the development of PH later in the course of the disease [35•]. The Pol3 antibody is seen with diffuse skin disease and renal crisis, but is rarely associated with significant lung fibrosis [35•].

The majority of patients with SSc-ILD have NSIP-pattern injury [36]. Less commonly, a UIP-pattern is observed, and other histophatological patterns (e.g., OP or DAD) are very rare. As with other CTD-ILD patients, a subset with SSc-ILD is believed not to require treatment. Some experts adhere to using a staging system to help determine which SSc-ILD patients to treat with immunomodulatory therapy: Goh and colleagues observed that patients with lung involvement greater than 20 % on HRCT and a FVC< 70 % of predicted were most likely to progress without therapy [37]. Such patients with more severe disease are often treated aggressively.

Two randomized placebo controlled trials, the **S**cleroderma **L**ung **S**tudy (SLS) and the **F**ibrosing **A**lveolitis **S**cleroderma **T**rial (FAST), evaluated cyclophosphamide (given orally at 2 mg/kg for one year in SLS, and intravenously at a dose of 600 mg/m2 monthly for six months, followed by oral azathioprine for the following six months in FAST) for SSc-ILD [14, 15]. Results from both studies demonstrated a slower decline in FVC in the cyclophosphamide group compared with placebo. Intravenous administration of cyclophosphamide was associated with a lower rate of gonadal failure, severe infections and bone marrow toxicity compared to oral medication, presumably due to higher cumulative dose achieved with daily oral medication [38]. Six months after discontinuation of immunosuppression, the improvements in FVC waned to baseline, suggesting prolonged immunomodulatory therapy may be required to maintain stability of lung function [39].

Whether there is a causal relationship between ILD and esophageal dysmotility/gastroesophageal reflux disease (GERD)/microaspiration is unclear, but we believe aggressive treatment of these abnormalities in patients with SSc-ILD (and any other ILD patient with them) is warranted. Co-management with gastroenterology can be helpful.

Polymyositis and dermatomyositis Both polymyositis (PM) and dermatomyositis (DM) share the diagnostic criteria of symmetrical proximal muscle weakness, raised serum muscle enzymes, and muscle biopsy and electromyography results consistent with myositis. In addition, DM requires the presence of certain skin manifestations (e.g., heliotrope rash and Gottron's sign) to fulfill diagnostic criteria [40, 41•]. In amyopathic DM, classical skin findings of DM are present without muscle involvement [42]. Overall, pulmonary disease is present in one-third to two-thirds of patients and is a significant cause of mortality in PM/DM [43•].

In patients with clinically significant disease, two main types of clinical presentations have been observed. The first is characterized by subacute onset of dyspnea and widespread basilar predominant ground-glass opacities and consolidation against a background of reticulation with traction bronchiectasis on CT [44•]. Many patients presenting this way progress significantly over a few weeks to months and are refractory to therapy. Histopathologically, a DAD pattern atop both OP and NSIP has been described in this setting [45, 46]. The other form of presentation is more common and involves an insidious onset and slowly progressive dyspnea. A combined pattern of NSIP and OP are observed on HRCT and in histopathological specimens [47-49]. Other patients with PM/DM can present with a UIP-pattern of lung injury.

As with most CTDs, lung involvement in PM/DM may occur before, after or at the same time of the development of extrapulmonary manifestations [50, 51]. Risk factors for the development of PM/DM-ILD include a higher age (>45), joint involvement [51, 52], and in particular, the presence of aminoacyl-tRNA synthetase (i.e., anti-synthetase or AS) antibodies. The most commonly identified AS antibody is directed against anti-histidyl-tRNA synthetase (anti-Jo1) and is present in 25–40 % of all patients with PM/DM [53•, 54, 55] and in 30–75 % of those cases with ILD [49, 52, 56-58]. Other less commonly found antibodies include anti-PL-7, -PL-12, -OJ, -EJ, -KS and -Zo [51, 55, 59]. The combination of arthritis, myositis, anti-synthetase antibodies and ILD constitutes the anti-synthetase syndrome. Raynaud's phenomenon, "mechanic's hands" (dry, rough, fissured skin of the hands, particularly on the thenar side of the index finger and the finger tips) and fever, while not part of the diagnostic criteria of anti-synthetase syndrome, are other findings frequently encountered [59]. It is not entirely clear whether AS antibodies are pathogenic or merely disease markers. In addition, it is unknown whether the different AS antibodies portend different clinical phenotypes.

As with most other CTDs, no definitive recommendations for the treatment of PM/DM-associated ILD exist due to the lack of randomized clinical trials. High-dose oral prednisone is often used as first-line therapy in PM/DM-associated ILD. In the US, azathioprine and mycophenolate

are the most frequently used immunomodulatory agents for PM/DM-ILD; however, there are case reports and case series suggesting a role for the calcineurin antagonists [60, 61]. In severe, rapidly progressive disease, intravenous cyclophosphamide in conjunction with high-dose methylprednisone has been used [62, 63]. Rituximab has been tried in patients who failed to respond to conventional immunosuppressive regimens or who presented with rapidly progressive DAD [64, 65]. In addition to treating refractory myositis, intravenous immunoglobulins have been used with some success to treat rapidly progressive ILD [66]. In PM/DM, the risk of malignancy is increased and screening for occult neoplasm should be considered, particularly in patient without AS antibodies.

Sjögren's syndrome In 1933 Sj gren introduced the term "keratoconjunctivitis sicca", also referred to as "sicca complex" to describe a syndrome characterized by dry eyes and dry mouth [67]. Sj gren's syndrome (SjS) is a chronic inflammatory condition characterized by lymphocytic infiltration of exocrine glands (including salivary and lacrimal glands), and other structures, including the lungs. It can occur either in isolation, when it is referred to as primary SjS, or as a secondary phenomenon in the setting of another established CTD, in which case it is termed secondary SjS [68•]. The primary form displays more severe exocrine dysfunction, including renal tubular disorder, neurological involvement and vascular disorders (Raynaud's phenomenon and vasculitis) [69]. In the absence of a salivary gland biopsy demonstrating focal lymphocytic sialoadenitis, the presence of "keratoconjunctivitis sicca" and anti-nuclear antibodies against ribonucleoproteins Ro/SSA and La/SSB is required to fulfill diagnostic criteria in both primary and secondary SjS [69]. Polyclonal hypergammaglobulinemia, elevated sedimentation rate and other autoimmune antibodies (e.g., rheumatoid factor) can be found with varying frequency in SjS and are nonspecific [70, 71]. Patients with SjS are at increased risk for pulmonary and other lymphomas [72•, 73].

Although restriction and reduced DLco have been found in 17–37.5 % of patients with SjS, clinically significant ILD is rare, and in most cases SjS-ILD follows a mild and self-limited course [74, 75]. Respiratory symptoms mostly relate to dry mucous membranes predisposing patients with SjS to hoarseness and dry cough (due to xerotrachea). Patients with SjS are at increased risk of respiratory tract infections, due to impaired immune function of the mucosal barrier lining the airway epithelium. Exertional dyspnea is reported by some patients [75, 76]. Pleuritis, PAH, middle lobe syndrome and shrinking lung syndrome have been described in SjS rarely [77•, 78-80].

Authors of older series reported LIP as the most common histopathological pattern in patients with SjS, but more recent studies have revealed a higher frequency of NSIP-pattern injury in this disease [81•, 82]. This finding is likely based on the reclassification of many cases as cellular NSIP, which in the past would have been interpreted as LIP [83]. Other less commonly observed patterns include OP and UIP. In patients with SjS-ILD, HRCT and histopathological findings correlate well with each other, so SLBx is usually not recommended [82, 84, 85]. However, radiographic features suggestive of lymphoma (see below) require thorough investigation [86•]. Ground-glass opacities and thin-walled cysts in a peri-bronchovascular distribution can occur with LIP. Centrilobular nodules are noted with LIP or lymphocytic bronchiolitis. Pulmonary lymphoma accounts for approximately 20 % of all SjS-associated lymphomas [73, 74]. Both LIP and pulmonary lymphoma have overlapping features, including ground-glass opacification, small nodules and hilar-mediastinal lymphadenopathy. Consolidation, large nodules measuring more than 10 mm, as well as pleural effusions, are more common in lymphoma, whereas cysts are more frequently observed in LIP [87].

Unclassifiable connective tissue disease

A large minority of patients with ILD do not fulfill the diagnostic criteria for any specific CTD, but display features including positive serologies and systemic extrapulmonary manifestations that are reminiscent of an underlying autoimmune disease. Such patients have been labeled as having an "autoimmune flavor" [87]. Over the course of follow-up, a number of these patients go on to develop clinical and serological characteristics that fulfill diagnostic criteria for a specific CTD [88•]. Ongoing investigations aim to determine how best to follow, treat and conduct research in this interesting population. Such patients are different from those with anti-U1 RNP antibodies and features of more than one specific CTD who have mixed connective tissue disease (MCTD)—a specific CTD [89•]. While a large number of patients with MCTD have pulmonary involvement, most have relatively mild disease, and many are asymptomatic [90]. Pleural effusions, ILD consistent with NSIP and sometimes UIP, and PAH, either as a result of CTD-ILD or in isolation, have all been described in MCTD [91•, 92].

Systemic lupus erythematosus SLE is a multisystem disorder afflicting joints, skin, kidneys, central nervous system, and serosal surfaces of internal organs including heart and lungs. The disease is more prevalent in women of reproductive age and African Americans [93]. Almost all patients are anti-nuclear antibody (ANA) positive [94, 95]. Four or more criteria are required to establish the diagnosis [96•]. Interestingly, these criteria do not include any pulmonary manifestations, except for pleuritis. Although respiratory symptoms associated with SLE are often absent, abnormal

PFT and HRCT findings are common, and the prognosis is significantly worse in patients experiencing pulmonary complications [97, 98•, 99, 100].

While trivial lung disease is present in one third of patients, clinically significant disease afflicts only 3–8 % of the lupus population [101, 102]. In some cases, acute lupus pneumonitis (ALP) with a DAD-pattern heralds the development of ILD [103]. Similar to most other CTD-ILDs, NSIP is the most commonly observed histopathological pattern, but LIP, OP and UIP have all been described [98•, 104-106]. Diffuse alveolar hemorrhage (DAH) and ALP are characterized by acute onset of dyspnea with fever, cough and in the case of DAH, sometimes hemoptysis. A sudden decrease in hemoglobin is highly suggestive of DAH [99, 104, 107, 108]. Approximately one-half of patients with DAH require mechanical ventilation. An increasingly bloody return on BAL is diagnostic and supported by high counts of red blood cells and hemosiderin-laden macrophages on the differential cell count. A neutrophilic capillaritis and alveoli filled with red blood cells are seen on histopathology of lung tissue from patients with DAH [109]. In ALP, the histopathological picture resembles DAD, but without hemorrhage or capillaritis [99]. Both ALP and DAH present with diffuse, bilateral ground-glass opacities on HRCT. In this setting pulmonary edema, drug reactions as well as infection all need to be excluded.

Due to the high incidence of infections in SLE, broad-spectrum antibiotic therapy should be started empirically without delay, while infectious etiologies are excluded and before aggressive immunosuppression is initiated. DAH and ALP carry a mortality rate of 50 % [104, 109]. In patients requiring mechanical ventilation, a lung protective strategy with low tidal volumes should be used. We recommend high-dose intravenous methylprednisone (1 g daily for 72 hours), followed by oral corticosteroids and possibly intravenous cyclophosphamide. In refractory cases of DAH or ALP, plasmapheresis and intravenous immunoglobulins have been described [99, 104]. Success with rituximab has also been reported [109].

Conclusions

CTD-ILD comprises a heterogeneous group of disorders marked by varying degrees of fibrosis and/or inflammation within the lung parenchyma. ILD is a potentially morbid and life-threatening complication of any CTD, but it is most commonly seen in patients with RA, SSc or PM/DM. A large group of patients have features suggestive of CTD, but cannot be classified according to currently available systems. How best to treat them—or other patients with CTD-ILD—is based largely on experience and observational studies. Future research is required to advance understanding of the pathogenesis of CTD-ILD and to help determine which patients require therapy, what drugs to use and how long to use them.

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- • Of importance
- •• Of major importance

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