

Collagen vascular disease-associated interstitial lung disease

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Abstract

Interstitial lung disease (ILD) is an important mani-

festation of collagen vascular diseases. It is a common feature of scleroderma, and also occurs in dermatomyositis and polymyositis, mixed connective tissue disease, Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, and Antineutrophil cytoplasmic antibody-associated vasculitis. When present, it is associated with increased morbidity and mortality, thus making early diagnosis important. In fact, in many patients, ILD may be the first manifestation of a collagen vascular disease. The most common symptoms are cough and dyspnea. The diagnosis is made based on pulmonary function tests showing restrictive lung disease and impaired oxygen diffusion and chest imaging showing ground glass infiltrates, interstitial thickening, and/or fibrosis. The most common histologic finding on lung biopsy is non-specific interstitial pneumonia, though organizing pneumonia and usual interstitial pneumonia may also be seen. Treatment is focused on addressing the underlying collagen vascular disease with immunosuppression, either with corticosteroids or a steroid-sparing agent such as cyclophosphamide, azathioprine, or mycophenolate, although the optimal agent and duration of therapy is not known. There are few clinical trials to guide therapy that focus specifically on the progression of ILD. The exception is in the case of scleroderma-associated ILD, where cyclophosphamide has been shown to be effective.

Key words: Interstitial lung disease; Collagen vascular disease; Connective tissue disease; Rheumatoid arthritis; Scleroderma; Myositis; Sjogren's syndrome; Systemic lupus erythematosus; Antineutrophil cytoplasmic antibody-associated vasculitis; Mixed connective tissue disease

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Core tip: Interstitial lung disease (ILD) is a significant manifestation of collagen vascular diseases due to its association with increased morbidity and mortality. Thus it is important for clinicians to consider and be able to recognize collagen vascular disease-associated

ILD and initiate appropriate treatment. This review will discuss the clinical features, histologic findings, and treatment options of collagen vascular disease-associated ILD.

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INTRODUCTION

Collagen vascular diseases (CVD) are a diverse group of autoimmune diseases which can have a myriad of manifestations. These include cardiac (pericarditis), musculoskeletal (myositis, inflammatory arthritis), dermatologic (rashes), ophthalmic (uveitis), and pulmonary [interstitial lung disease (ILD), pulmonary arterial hypertension]. ILD is a frequent manifestation of CVD, although the prevalence varies between each disease. ILD is most commonly seen in scleroderma, where it is found in up to 70% of patients, and least commonly in lupus where it occurs in 5%-10% of patients^[1-4]. ILD may also be the initial presentation of a CVD. Based on the experience at the Johns Hopkins ILD clinic, 15% of patients presenting with a new diagnosis of ILD have an undiagnosed CVD^[5]. Regardless of the associated CVD, when ILD does occur, it is associated with increased morbidity and mortality^[3,4,6-14]. Thus it is critical that ILD is identified early so that treatment can be initiated. In this review, the clinical presentations, histologic features, and treatment of collagen vascular disease-associated ILD (CVD-ILD) will be discussed. A summary of the key features of CVD-ILD can be found in Table 1.

OVERVIEW

Clinical presentation

Clinically, ILD typically manifests with progressive dyspnea on exertion and dry cough. However, given the existence of concomitant joint disease and mobility issues, patients often attribute the early symptoms to the CVD or deconditioning and have frequently lost considerable lung function prior to diagnosis. CVD-ILD is diagnosed based on clinical presentation, loss of lung function and demonstration of interstitial scarring on chest imaging. Pulmonary function testing (PFT) reveals restrictive lung disease with diminished total lung capacity (TLC), decreased forced vital capacity (FVC), and impaired diffusion capacity of the lung for carbon monoxide (DLCO). Chest imaging demonstrates ground glass, inter- and intra-lobular interstitial thickening, and in many cases end stage fibrosis and scarring^[15]. Imaging may also show other manifestations of the underlying CVD such as

enlargement of the pulmonary artery or dilation of the esophagus^[15]. Bronchoscopy is often used to rule out alternative diagnoses such as infection but is not typically diagnostic of CVD-ILD.

Histology and imaging findings

Lung biopsy may show a variety of histopathology, most commonly non-specific interstitial pneumonia (NSIP), though organizing pneumonia (OP) and usual interstitial pneumonia (UIP) may be present depending on the CVD^[16]. However, due to the risks of the procedure, surgical lung biopsy is not routinely part of the workup of CVD-ILD. Diagnosis is based upon clinical presentation, history, PFTs and high-resolution computed tomography (HRCT) scan. The typical HRCT findings for a patient with UIP are intralobular septal thickening, honeycombing, traction bronchiectasis, and subpleural, peripheral reticular opacities^[17]. In contrast, NSIP is characterized by subpleural ground glass opacities, predominantly in the lower lobes^[17]. There may be interlobular septal thickening and honeycombing, but the honeycombing is typically microcystic^[17]. In OP, the HRCT shows patchy, peripheral ground glass opacities or consolidations, which may be migratory^[17]. Lymphoid interstitial pneumonia (LIP) is characterized by diffuse ground glass opacities with intermixed central or perivascular cysts^[17]. Thus, HRCT is essential in not only diagnosing CVD-ILD but also in suggesting potential histologic patterns that may alter prognosis.

Due the association between esophageal dysmotility and CVD, particularly in patients with scleroderma, there can also be evidence of chronic aspiration in the lungs. Studies have found that chronic aspiration is associated with a bronchocentric distribution of noncaseating granulomas, basophilic intraluminal contents and foreign-body containing multinucleated giant cells on histopathology^[18-21]. On HRCT, patients with chronic aspiration have centrilobular nodules, tree-in-bud opacities, and bronchial wall thickening with or without fibrosis, predominantly in the lower lobes, often times with dilation of the esophagus as well^[18-21].

Treatment

Generally speaking, treatment of CVD-ILD is focused on addressing the underlying CVD, and there are not many randomized-controlled trials looking at the ILD specifically to guide therapy. The exception to this is in the case of scleroderma-associated ILD, where studies have shown cyclophosphamide to be effective^[22,23].

FEATURES OF SPECIFIC CVD-ILD

Clinical presentation

Scleroderma is a CVD with skin, cardiac, pulmonary, gastrointestinal, and renal involvement^[24]. The pulmonary manifestations include pulmonary arterial

Table 1 Summary of key features of collagen vascular-interstitial lung disease

	Prevalence	Histology	Other pulmonary findings	Treatment
Scleroderma	> 70%	NSIP	Pulmonary arterial hypertension	¹ Cyclophosphamide ^[22,29] Mycophenolate, azathioprine used for maintenance
Dermatomyositis/ Polymyositis	20%-30%	NSIP	Diaphragmatic weakness	Corticosteroids Azathioprine Mycophenolate Calcineurin inhibitors Rituximab IVIg
Mixed connective tissue disease	30%-60%	NSIP	Diaphragmatic weakness	Corticosteroids ± cyclophosphamide
Sjogren syndrome	25%-40%	NSIP, UIP, OP, LIP		Corticosteroids ± cyclophosphamide
Rheumatoid arthritis	10%-20%	UIP	May have obstructive lung disease, necrobiotic nodules, pulmonary arterial hypertension	Corticosteroids ± cyclophosphamide or azathioprine
Systemic lupus erythematosus	5%	NSIP, OP	Pulmonary arterial hypertension, Pleural effusion	Corticosteroids ± cyclophosphamide or azathioprine
ANCA-associated vasculitis	7%-47%	UIP	Pulmonary hemorrhage	Induction with corticosteroids + cyclophosphamide or rituximab ^[84-86] Maintenance with methotrexate or azathioprine Plasmapheresis for pulmonary hemorrhage

¹Use in collagen vascular disease-associated- interstitial lung disease supported by multicenter clinical trials.

hypertension and ILD^[24]. ILD is a significant cause of mortality in patients with scleroderma^[6,7,13]. Lung involvement portends a worse prognosis, and more severe fibrosis is correlated with higher mortality^[6,7,12,13]. The prevalence of pulmonary fibrosis varies between studies. When diagnosed by either restrictive physiology on PFTs or characteristic findings on HRCT scan, ILD is present in 25%-40% of patients^[12,13,24,25]. However, this likely underestimates the true prevalence of disease as at autopsy, ILD is present in at least 70% of cases^[1,16]. Due to its association with pulmonary arterial hypertension and esophageal dysmotility, other common findings on HRCT scan are enlargement of the pulmonary artery and dilation of the esophagus^[15]. PFTs may also show evidence of pulmonary arterial hypertension with reduction in DLCO out of proportion to the reduction in TLC.

Histology and imaging findings

The most common histopathology pattern is NSIP. Rarely UIP or OP are seen^[16,26,27]. HRCT most commonly shows confluent ground glass, a fine reticular pattern of interstitial markings, and traction bronchiectasis^[15].

Treatment

The most established treatment for scleroderma-associated ILD is cyclophosphamide^[28]. In two multicenter randomized placebo-controlled trials, treatment with cyclophosphamide for one year showed improvement in lung function^[22,29]. In the Scleroderma Lung Study, cyclophosphamide was shown to improve FVC and TLC after 12 mo of therapy compared to

placebo^[22]. Follow up analysis of this study identified a group of patients with an enhanced response to treatment, who were characterized by more severe fibrosis at baseline based on HRCT scan and/or more severe skin involvement^[23]. The other study compared prednisolone plus cyclophosphamide for 6 mo followed by azathioprine and found at 12 mo a trend towards improvement in FVC^[29]. Other studies have shown similar results^[30-33]. One question that remains, however, is the optimal duration of treatment. The Scleroderma Lung Study found that following 12 mo of therapy, the benefit persisted 6 mo after treatment was stopped, with lung function returned to pre-treatment levels 12 mo after therapy was ended^[22,23]. Additional studies with longer follow up have shown persistent stability in lung function up to 3-4 years after the end of therapy^[32,34]. However, not all patients have such a prolonged benefit. One study found that 4 years after therapy, although 69% of patients had stable lung function, 32% of patients had experienced progression of their disease^[32]. Due to the side effects of cyclophosphamide, other drugs have been explored for use as maintenance therapies. Azathioprine and methotrexate are commonly used as maintenance^[26,33,35,36]. However, concern remains of using methotrexate in patients with CVD-ILD as the drug itself may cause drug-induced-ILD that may complicate the picture.

As monotherapy, mycophenolate has also been shown in retrospective studies to stabilize lung function after at least 6 mo of therapy^[37-39]. Azathioprine as monotherapy was shown to stabilize FVC and improve dyspnea after treatment for at least 12 mo in a

retrospective study^[40]. However, a subsequent study comparing cyclophosphamide to azathioprine showed worsening of lung function with azathioprine compared to stability of lung function with cyclophosphamide^[41].

Due to the association between corticosteroids and scleroderma renal crisis, corticosteroids have been used less commonly than for other CVD-ILD. However, a retrospective cohort analysis of two medical centers in Japan showed that corticosteroid monotherapy as compared to no therapy was associated with improvement in FVC without any change in 5 or 10-year survival^[42].

Another medication that has been evaluated is rituximab. Rituximab is a monoclonal antibody against B cells and has been shown in a few case reports and one randomized controlled trial of 14 patients to be associated with improvement in lung function^[43].

Recently, pirfenidone has been shown in patients with idiopathic pulmonary fibrosis (IPF) to slow decline in FVC^[44]. Pirfenidone has antifibrotic effects, and in mouse models of IPF has been shown to reduce pro-fibrotic cytokines such as transforming growth factor beta (TGF- β) and to inhibit fibrocyte accumulation in the lungs^[45,46]. This drug is now being studied in patients with scleroderma-ILD to see if it has the same effects as in patients with IPF.

These trials have not examined responses based on histology patterns, as most patients do not require a lung biopsy to make the diagnosis. One exception is in patients who have fibrotic lung disease with predominantly features of chronic aspiration. Esophageal dysmotility, which can predispose one to chronic aspiration, is a common feature of scleroderma. One study differentiated patients with scleroderma-ILD into those with features of NSIP vs those with features of chronic aspiration based on lung biopsy, with those found to have NSIP treated with cyclophosphamide for one year and those found to have chronic aspiration treated with aggressive proton pump inhibitor therapy, prokinetic medications, and lifestyle modifications for GERD^[21]. After one year of therapy, both groups had stability in their FVC, FEV1, and DLCO, suggesting that in a subset of patients with ILD related to chronic aspiration, antireflux therapy may be critical in slowing or halting disease progression^[21].

DERMATOMYOSITIS AND POLYMYOSITIS

Clinical presentation

ILD is also commonly found in patients with dermatomyositis and polymyositis, and is a significant cause of mortality^[9,10,14]. Studies have found that 20%-30% of patients with myositis have ILD, and ILD may precede muscle and skin findings in about 20% of patients^[9,10,14,47]. There is a strong association between ILD and the presence of antisynthetase antibodies (most commonly

anti-Jo-1)^[9,10,47]. Because of associated muscular weakness and deconditioning, dyspnea on exertion may go unrecognized for some time. Additionally, muscular weakness can affect the diaphragm, causing a diminished TLC out of proportion to the DLCO, which is more pronounced in the supine position.

Histology and imaging findings

The most common histology is NSIP, but OP or UIP may also be seen^[10,16,26]. HRCT typically shows confluent ground glass consolidation in the lower lobes with reticular interstitial changes and traction bronchiectasis, consistent with NSIP^[15].

Treatment

Treatment is based on the underlying histologic pattern. Organizing pneumonia and NSIP are most responsive to steroids compared to UIP^[10,26]. For those patients who do not respond to corticosteroids, retrospective studies and case series have shown stabilization or improvement in pulmonary function with the use of cyclophosphamide^[47,48], mycophenolate^[39,49], azathioprine^[14,50], and calcineurin inhibitors^[51-53]. Azathioprine and mycophenolate are also used for maintenance therapy following cyclophosphamide^[10]. Case reports have also shown improvement with intravenous immunoglobulin (IVIG)^[54,55].

MIXED CONNECTIVE TISSUE DISEASE

Clinical presentation

Mixed connective tissue disease (MCTD) is a unique collagen vascular disease characterized by the presence of anti-ribonucleoprotein (anti-RNP) antibodies and clinical features similar to lupus, scleroderma, and dermatomyositis/polymyositis, including myositis, sclerodactyly, Raynaud's phenomenon, and polyarthritides^[8,56,57]. ILD is present in approximately 30%-60% of patients^[8,57]. As in other CVD, the presence of severe fibrosis has been associated with increased mortality^[8]. In addition to ILD, MCTD is also associated with pleural thickening, pleural effusions, and pericardial effusions, all of which may be seen on HRCT scan^[15].

Histology and imaging findings

The most common pathology seen is NSIP, with UIP and OP seen less commonly^[16,26]. HRCT shows ground glass predominantly in the lower lobes^[15].

Treatment

Similar to other CVD-ILD, therapy is guided by treatment of the underlying CVD. Corticosteroids have shown some efficacy, with one uncontrolled study showing that 50% of patients treated with corticosteroid monotherapy had improvement in lung function, and an additional 20% improving with corticosteroids plus cyclophosphamide^[57].

SJOGREN'S SYNDROME

Clinical presentation

Sjogren's syndrome is a disease primarily affecting exocrine glands, with ILD representing a major extraglandular manifestation^[11]. Studies have found a wide range in the prevalence of ILD, from 25%-40%^[11,58-60]. As with other CVD-associated ILD, the presence of ILD is associated with poor survival^[11].

Histology and imaging findings

The most common pathology pattern is NSIP, but UIP, OP, and LIP can be present as well^[16,26,61-63]. The typical HRCT findings are consistent with NSIP, patchy ground glass and microcystic honeycombing predominantly in the lower lobes^[15]. When LIP is present, the HRCT shows ground glass, cysts (5-30 mm), and peribronchovascular, centrilobular, and subpleural nodules^[15]. Other findings that can be seen in patients with Sjogren's syndrome in general are bronchial wall thickening, bronchiectasis, air trapping, cysts, and nodules^[15].

Treatment

Corticosteroids are the primary treatment, with case series showing the majority of patients improving with this therapy^[61]. There are also reports of corticosteroid and cyclophosphamide used with the majority of patients demonstrating improvement or stabilization of lung function^[63].

RHEUMATOID ARTHRITIS

Clinical presentation

ILD is the most common pulmonary manifestation of rheumatoid arthritis (RA), affecting approximately 10%-20% of patients^[3,4,64-66]. Development of ILD is associated with increased mortality^[3,4]. Although most patients with rheumatoid arthritis are women, male gender confers an increased risk of developing ILD^[64,67,68]. Smoking, anti-citrullinated protein (anti-CCP) antibodies, and rheumatoid factor (RF) antibodies have also all been associated with an increased risk of developing ILD^[3,68,69]. In addition to ILD, pulmonary manifestations of rheumatoid arthritis include pulmonary arterial hypertension, necrobiotic nodules, and obliterative bronchiolitis, and thus HRCT may show enlargement of the pulmonary artery, mosaic attenuation with air trapping, and/or pulmonary nodules^[15]. On PFTs, reduction in DLCO out of proportion to the reduction of TLC suggests the presence of pulmonary arterial hypertension as well. There also may be obstruction if there is concomitant airways disease.

Drugs used to treat RA have also been associated with pulmonary toxicity, and it is important to differentiate between drug-induced lung disease and RA-ILD. Agents known to cause pulmonary toxicity include methotrexate, gold, penicillamine, leflunamide,

and anti-tumor necrosis factor alpha (anti-TNF- α) agents^[65,70-72]. Indeed, biologic agents, specifically anti-TNF- α agents have been associated with both new and exacerbation of underlying ILD^[73]. Increased mortality rates in up to two-thirds of patients with existing ILD were reported^[73]. It is unclear if the drugs caused the worsening ILD or that the patients had underlying aggressive disease necessitating use of more aggressive ILD therapy with biologic agents. Drug-induced pulmonary toxicity should be suspected based on the timing of symptoms and use of a suspect medication. Labs may or may not be helpful. In the case of penicillamine, patients develop a peripheral eosinophilia, but in the case of other drugs, labs and BAL findings are nonspecific^[72]. The treatment is to stop the offending agent and in severe cases start steroids.

Histology and imaging findings

Unlike the other CVD, UIP is the most common histopathology, though NSIP can also be seen^[16,26,71]. The UIP pattern is associated with an increased mortality and a poor response to therapy compared to the NSIP pattern^[68,74]. However, the prognosis with a UIP pattern associated with rheumatoid arthritis is less severe than in patients with IPF^[74]. HRCT findings in RA-ILD are most commonly a UIP pattern, similar to IPF, with basal predominant, subpleural, peripheral distribution of interstitial fibrosis and honeycombing^[15]. Given that it does not change management, surgical lung biopsy is not typically performed to differentiate between UIP and NSIP.

Treatment

For patients with NSIP and OP pathology, corticosteroids are first line therapy^[71,75]. However, UIP has not been shown to be steroid responsive^[71]. Typically patients are treated with a combination of corticosteroids and cyclophosphamide, or corticosteroids and azathioprine, though there are not studies to evaluate the efficacy of these regimens^[70]. Medications used for RA that are associated with causing lung injury or worsening ILD should be avoided^[70]. As noted above, due to concerns with anti-TNF- α either initiating or exacerbating ILD, there have yet to be any clinical trials evaluating use of biologic anti-TNF- α agents to treat RA-ILD.

SYSTEMIC LUPUS ERYTHEMATOSUS

Clinical presentation

Systemic lupus erythematosus (SLE) can have a variety of pulmonary manifestations, including pleuritis with or without a pleural effusion, pulmonary arterial hypertension, thromboembolic disease, and diaphragmatic weakness^[76]. ILD is a rare manifestation of lupus, occurring in approximately 5%-10% of patients^[2]. However, this number may underestimate the true prevalence, as an autopsy study revealed a

prevalence of approximately 15%^[77]. Other studies have found evidence of ILD on HRCT in up to 30% of patients^[78].

SLE patients can also develop an acute pneumonitis, characterized by acute onset of fever, dyspnea, cough, and pleuritic chest pain^[76,78]. HRCT shows diffuse ground glass and consolidations^[15,76,78]. Patients with acute pneumonitis are critically ill, and there is a high mortality rate. Treatment is based on case reports, and high dose corticosteroids are most commonly used^[76].

Histology and imaging findings

SLE-ILD is associated with an NSIP or OP pattern^[16,26]. HRCT shows subpleural ground glass opacities, or patchy consolidation and air bronchograms consistent with NSIP or OP respectively^[15].

Treatment

There are no placebo-controlled trials to guide treatment for lupus-associated ILD^[76,78]. Corticosteroids have been used with some efficacy in slowing or improving ILD^[2]. Other immunosuppressants such as azathioprine and intravenous cyclophosphamide have also been used^[76].

ANCA-ASSOCIATED VASCULITIS

Clinical presentation

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are pauci-immune vasculitides that includes granulomatosis with polyangiitis (GPA, formerly called Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGP, formerly called Churg-Strauss syndrome). These conditions, particularly MPA, have been associated with ILD. Studies have found the prevalence of ILD in patients with MPA to range from 7%-47% of patients^[79-81]. The presence of myeloperoxidase-ANCA (MPO-ANCA) rather than proteinase 3-ANCA (PR3-ANCA) is associated with ILD^[80]. Other pulmonary manifestations of AAV are pulmonary hemorrhage, pulmonary nodules, and tracheobronchial stenosis or masses^[79,81]. Asthma is also a feature of EGP.

Histology and imaging findings

On histology, the most common pattern is UIP, with NSIP also seen, as well as vasculitis of bronchial and pulmonary arterioles^[82]. HRCT typically shows a UIP or NSIP pattern, with thickened interlobular septa, honeycombing, traction bronchiectasis and ground glass infiltrates^[79,81,82].

Treatment

The mainstay of treatment of ANCA-associated vasculitis is induction therapy with either cyclophosphamide and prednisone or rituximab and prednisone, followed by maintenance with methotrexate or azathioprine^[83-87].

Plasmapheresis is used only for patients with severe pulmonary hemorrhage^[87].

CONCLUSION

ILD is a manifestation of CVD that causes significant morbidity and mortality. It typically presents with dyspnea and cough, though due to other symptoms such as systemic weakness and deconditioning, symptoms may become apparent only after significant lung function has been lost. The most common histology is NSIP, although OP and UIP are also seen^[16]. UIP is most commonly seen in RA-ILD and AAV-ILD and is associated with less response to treatment and worse prognosis compared to NSIP^[16,26,71,82]. In terms of therapy, the only randomized-controlled trials are in patients with scleroderma-associated ILD, where cyclophosphamide has been shown to be effective in halting progression of disease^[22,29]. For other CVD-ILD, therapy is targeted at controlling the underlying CVD, most commonly with steroids, cyclophosphamide, mycophenolate, and azathioprine. Given the significant morbidity and mortality associated with CVD-ILD, future studies are needed to evaluate the optimal therapy for these diseases. Additionally, it is important to explore the pathogenesis underlying development of ILD in order to provide future targets for new therapies.

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