Pulmonary Manifestations of Connective Tissue Diseases

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Abstract

Pulmonary involvement in connective tissue diseases (CTDs) often causes significant morbidities and mortalities. During disease course, most patients with connective tissue diseases show signs of involvement of the lung, vasculature, the pleura, and the diaphragm. Pleurisy, coughing, and dyspnea are often the first clues to make the diagnosis. Interstitial lung disease is the most frequent pulmonary manifestation. Differential diagnosis includes respiratory infection and medication-associated lung toxicity. In some asymptomatic patients, abnormal pulmonary function tests (PFTs), including the diffusing capacity for carbon monoxide (DLCO) or abnormal chest high resolution CT (HRCT), may be presented. Descriptions of radiologic patterns and pathologic findings used in the idiopathic interstitial pneumonias are now being applied to patients with CTDs. Corticosteroid or immunosuppressant may be administered based on the disease severity. (J Intern Med Taiwan 2015; 26: 177-185)

Key Words: Connective tissue diseases (CTDs), Interstitial lung disease (ILD), Systemic lupus erythematosus (SLE), Rheumatoid arthritis (RA), Sjögren syndrome (SjS), Systemic sclerosis (SSc), Dermatomyositis (DM) / polymyositis (PM)

Connective tissue diseases (CTDs) contain a heterogeneous group of autoimmune disorders characterized by the presence of autoantibodies and autoimmune-mediated organ damage. They include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren syndrome (SjS), systemic sclerosis (SSc), dermatomyositis (DM) / polymyositis (PM), mixed connective-tissue disease (MCTD), etc.

Serological testing is primarily applied to confirm a specific diagnosis and, in some cases, to evaluate disease activity relative to CTDs. Based on a high index of clinical suspicion, physicians should have a compelling reason to order serologic autoantibody tests to diagnose CTD (Table 1).

Many CTDs involve the lungs either directly or as a complication of treatment of the CTDs. Several different components of the respiratory system may be involved, including the airways, vessels, parenchyma, pleura, and respiratory muscles[1]. A comprehensive evaluation is indicated for CTD patients with respiratory symptoms to explore a wide range differential diagnosis that includes respiratory infection, medication-associated lung toxicity, autoimmune mediated lung injury, and cardiovascular

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complications. Different CTDs had varied incidence and prevalence of each component of the respiratory tract. (Table 2). Interstitial lung diseases (ILD) are common pulmonary complications of the CTDs.

Some evidence suggests that the incidence of ILD is increasing in CTDs patients. Recent studies have shown radiographic prevalence rates of subclinical ILD ranging from 33% to 57%[5-7]. This increment may be related to an increased use of diagnostic bronchoscopy, high-resolution computed tomography (HRCT), pulmonary function tests (PFTs), and video-assisted thoracoscopic surgery.

ILD associated with CTDs may consist of several histological subtypes. Each had different clinical manifestation and radiologic finding[8] (Table 3).

CTD-related ILD have a better prognosis than idiopathic ILD. Usually, they are more indolent in progression than IPF. An exception is RA-related ILD with UIP findings. However, mortality is high in patients with CTDs who develop ILD and pulmonary hypertension. In patients with RA and SLE who develop ILD, mortality is 3-4 times higher than that in the general population. The median survival of all patients with RA-related ILD has been reported to be approximately 5 years[9].

PM/DM and systemic sclerosis are associated with higher mortalities than other CTDs. Acute progressive subtype usually lead to high mortality than chronic subtype. Kang et al found that in Korean patients with PM/DM, ILD was observed in 40.3% and was associated with poor survival[10]. The 3-year

Table 1. Autoantibodies in Connective tissue diseases[1,2]

Autoantibody	RA	SLE	SSc	SjS	PM/DM	MCTD
RF	+	+	+	+	Rare	+
ANA	+	+	+	+	Rare	+
ds-DNA	-	+	-	-	-	-
Anticentromere	-	-	+	Rare	Rare	-
Scl-70	-	-	+	-	Rare	-
Anti-Jo	-	-	-	Rare	+ (ILD)	-
Smith antibody	-	+	-	-	-	-
Anti-Ro/SSA and anti-La/SSB	-	+	-	+	-	-
Anti-U1-RNP	-	-	-	-	-	+
Anti-CCP	+	-	-	-	-	-

ANA = antinuclear antibody; DM = dermatomyositis; ds-DNA = double-stranded DNA antibody; ILD = interstitial lung disease; MCTD = mixed connective-tissue disease; PM = polymyositis; RA = rheumatoid arthritis; RF = rheumatoid factor; RNP = ribonucleoprotein; SSc = systemic sclerosis; SLE = systemic lupus erythematosus; SjS = Sjögren syndrome; CCP = cyclic citrullinated peptide.

Table 2. CTDs and pulmonary manifestations[3,4]

	ILD	Airways	Pleural	Vascular	DAH
Systemic sclerosis	+++	-	-	+++	-
Dermatomyositis/ Polymyositis	+++	-	-	+	-
Rheumatoid arthritis	++	++	++	+	-
Sjögren's syndrome	++	+++	+	+	-
Systemic lupus erythematosus	+	+	+++	++	++
MCTD	++	+	+	++	-

The number of + signs indicates relative prevalence of each manifestation.
DAH = diffuse alveolar hemorrhage.

survival rate for patients with systemic sclerosis and pulmonary hypertension is 56%.

Specific CTDs

Each CTD have its common component of pulmonary involvement.

Systemic Lupus Erythematosus

SLE is characterized by autoantibody positivity and immune-mediated damage to different organ systems. It affects more often in women than in men.

Pleuritis and pleural effusions are the most common pulmonary manifestations of SLE[11]. Pleuritis is also one of the American College of Rheumatology classification criteria for SLE[12]. Less commonly, lupus pneumonitis, pulmonary hemorrhage, chronic interstitial fibrosis, and venous thromboembolic may present. Infections are also common and frequently lethal pulmonary complications of SLE.

Patients with SLE and lung involvement must always be evaluated for infection, particularly that due to bacteria or viruses. Besides, tuberculosis, fungal infections, and opportunistic infections should also be considered in immunocompromised hosts[13].

Pleural Disease

Pleuritic chest pain occurs in 30% to 60% of patients during the course of disease[14]. The chest pain is aggravated by deep breathing, motion or by change of position, and elicited by palpation of the painful areas. Pleural effusions are likely to be bilateral, small to moderate in size, and exudative. The pleural effusion in SLE is more likely have a normal glucose and pH and lower lactate dehydrogenase levels. A diagnostic thoracentesis is often indicated for new effusion because other cause must be excluded including infection, pulmonary embolism, and congestive heart failure. Pleural disease in SLE often responds to therapy with nonsteroidal anti-inflammatory drugs (NSAIDs). If there is no response within a few days, moderate- to high-dose glucocorticoids will be used. More severe disease may be required immunosuppressive agents.

Table 3. Classification of Idiopathic Interstitial Pneumonias[5,8]

Major idiopathic interstitial pneumonias
idiopathic pulmonary fibrosis (IPF) / Usual interstitial pneumonia (UIP)*
idiopathic nonspecific interstitial pneumonia (NSIP)
Desquamative interstitial pneumonia (DIP)
Cryptogenic organizing pneumonia (COP)
Acute interstitial pneumonia (AIP)
Rare idiopathic interstitial pneumonias
Idiopathic lymphoid interstitial pneumonia (LIP)
idiopathic pleuroparenchymal fibroelastosis
Unclassifiable idiopathic interstitial pneumonias

*The histopathological pattern of idiopathic pulmonary fibrosis is usual interstitial pneumonia (UIP).

DAH

Diffuse alveolar hemorrhage is one of the life-threatening pulmonary manifestations of SLE. DAH is and infrequent, occurring in less than 4% of hospital admission for SLE[15]. The most common symptoms included dyspnea, hemoptysis, and cough. The absence of hemoptysis should not exclude the diagnosis, approximately half of patients do not present with it. The bleeding may lead to anemia. Patients with DAH often have active concurrent extrapulmonary disease with the most common being lupus nephritis. Chest radiography usually revealed bilateral alveolar infiltrates, compatible with pulmonary edema or infection[16]. The diagnosis can be confirmed with sequential bronchoalveolar lavage samples revealing persistently bloody fluid with hemosiderin-laden macrophages, and adequate culture result may exclude infection. The most common underlying histologic pattern on surgical lung biopsy is capillaritis. Treatment with high-dose glucocorticoids in combination with cyclophosphamide, and aggressive supportive measures has significantly decreased mortality in some studies. In addition, the administration of plasmapheresis to

refractory cases may result in survival reported case series[17].

Thromboembolic Disease

Antiphospholipid antibodies (aPL) are common in SLE, occurring in approximately one-third of patients. Their presence is associated with an increased risk of vascular thrombosis and fetal loss. In patients with SLE and aPL, the risk of thrombosis is approximately 6 times that of patients without aPL[18]. The aPL has been associated with pulmonary arterial hypertension (PAH), diffuse alveolar hemorrhage (DAH), and diffuse alveolar damage (DAD)[19].

Rheumatoid Arthritis

RA is an autoimmune disease characterized by chronic symmetric erosive and inflammatory polyarthritis[20]. The disease typically affects women twice as often as men and the peak incidence is between the fourth and sixth decades. It may have some extra-articular manifestations, such as pleuropulmonary involvement, episcleritis, vasculitis, pericarditis, neuropathies and subcutaneous nodules. The risk of pulmonary involvement includes smoking, male gender, severe erosive joint disease, positive rheumatoid factor (RF) and the presence of other extra-articular manifestations.

Bronchiectasis

Bronchiectasis is common by HRCT and has been reported to affect 58% of patients with early RA[21]. The common symptoms include dyspnea, cough, hemoptysis, and recurrent infections and pulmonary function test often showed airway obstruction including a reduced forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Bronchiectasis is more common in long-standing RA, and mortality from recurrent infections and respiratory failure have been reported.

Pleural Disease

Pleural disease is common in patients with RA, but it is usually subclinical. Asymptomatic pleural effusion may be present in 70% of patients, whereas symptomatic effusions occur in approximately 5%[22]. It is more common in men and coexists with rheumatoid nodules and high rheumatoid factor titers. A diagnostic thoracentesis should be performed in patients with RA having symptomatic pleural effusion to exclude other etiology. The characteristics of RA pleural effusions include white cell count <5000/mm3, a decreased pleural fluid glucose (a pleural fluid to serum glucose ratio less than 0.5), a pH less than 7.3, high pleural fluid LDH level (greater than 700 IU/L), and elevated RF titer[23].

Interstitial Lung Disease

ILD is the most common pulmonary manifestation in RA. It is a source of substantial morbidity and mortality for affected patients. The presence of clinically significant ILD has been described in approximately 7% of patients[24]. In studies using chest high resolution computed tomography scanning screening for ILD in RA patients revealed a prevalence of almost 20%[25]. Others, RA-associated ILD is more common in men. High rheumatoid factor titers have been associated with the presence of ILD and with a reduction in the carbon monoxide diffusing capacity (DLCO)[26].

The common histopathological patterns of RA-associated ILD are usual interstitial pneumonia and nonspecific interstitial pneumonia (44-56 and 33-44%, respectively)[27,28]. Organizing pneumonia, DAD, lymphocytic interstitial pneumonia, and desquamative interstitial pneumonia histologic patterns have also been described.

The common symptoms are dyspnea on exertion and non-productive cough. The physical examination may reveal dry crackles on the pulmonary auscultation. The diagnosis of ILD in RA is based on the combination of clinical pulmonary symp-

toms, consistent PFTs and typical radiological findings. A histological study may be necessary in some patients. Fibrobronchoscopy and bronchoalveolar lavage (BAL) may be useful for making the differential diagnosis with other interstitial lung diseases, and for excluding pulmonary infections or drug-induced diseases.

Systemic Sclerosis (Scleroderma)

Systemic sclerosis (SSc) is a systemic autoimmune disease that is characterised by endothelial dysfunction resulting in a small-vessel vasculopathy, and excessive collagen production and fibrosis. Lung disease is common in systemic sclerosis and more than 50% patients are involved. Pulmonary manifestations including interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the leading cause of death[29]. These manifestations alone account for 60% of SSc-related deaths[30]. Interstitial lung disease or pulmonary arterial hypertension is also one of the 2013 classification criteria for systemic sclerosis by the American College of Rheumatology and European League against Rheumatism[31].

The cardinal feature of SSc is thickening of the skin and the extent of cutaneous involvement defines its subtypes. Patients with limited cutaneous SSc typically have skin thickening restricted to limbs below the elbows and knees and, to a lesser extent, to the face and neck. Diffuse cutaneous SSc is defined by more proximal and extensive skin thickening that includes skin changes proximal to the elbows or knees or involving the trunk[32]. Patients with diffuse cutaneous SSc present more acutely with a variety of symptoms including diffuse skin thickening, digital edema and arthritis. These patients are at high risk for early progressive ILD and scleroderma renal crisis. SSc-specific anto-antibodies revealed particular presentations of lung disease. Those with anticentromere antibodies have the highest risk for PAH and are at less risk for ILD. In contrast, those with anti–Scl-70 (anti-topoisomerase) antibodies are at highest risk for progressive ILD and a lower risk for PAH[33].

Vascular Disease

Systemic sclerosis is the connective tissue disease that is most often associated with PAH. Its prevalence varies depending on the series consulted, from 7% to 50%[34]. Approximately one third of patients are asymptomatic and dyspnea on exertion and fatigue are the two most common symptoms of PAH. Risk factors of SSc-PAH includes longstanding Raynaud's phenomenon (>8 years), limited cutaneous systemic sclerosis, extensive telangiectasia, positive anticentromere antibody, isolated positive nucleolar-pattern ANA or reduction in diffusing capacity for carbon monoxide (DLCO) in the absence of extensive ILD[35]. Survival of patients with SSc-PAH in the modern treatment era is better. Recent study reported one- and 3-year survival rates were 78 and 47% for patients with isolated SSc-PAH[36].

Interstitial Lung Disease

ILD is more often in SSc than in any other CTD. Most patients with SSc have radiologic evidence of ILD and about one-half of cases developed clinically significant ILD[37]. A cohort study of 3,656 SSc patients revealed ILD in 53% of cases with diffuse cutaneous SSc and in 35% of cases with limited cutaneous SSc[38]. The most common histologic pattern seen in SSc-associated ILD is nonspecific interstitial pneumonia (NSIP), and the usual interstitial pneumonia (UIP) pattern is less common[39,40]. HRCT characteristically reveals ground glass opacities, increased reticular markings, basilar prominence and minimal honeycombing consistent with an NSIP pattern. In contrast, the UIP pattern of SSc is characterized by patchy reticular opacities associated with traction bronchiectasis and honeycombing with a predominantly basal and peripheral reticular pattern.

In SSc, data from clinical studies and accumulated experience indicate that prognostic evaluation should focus on three factors: the duration of systemic disease, recent progression of ILD and the severity of ILD. The greatest risk of progression of SSc-ILD occurs during the first 4 years of systemic disease. A decrease in FVC in this period is strongly predictive of the eventual development of major ILD[41].

Primary Sjögren's Syndrome

Sjögren's syndrome (SjS) is a slowly progressive autoimmune inflammatory disease characterized by lymphocytic infiltration of the exocrine glands that diminishes glandular function and causes mucosal dryness. The salivary and lacrimal glands are most often affected leading to the characteristic symptoms of disease including dry eyes (keratoconjuctivitis sicca) and dry mouth (xerostomia). Its prevalence is 0.5%-1% and women are more commonly affected. Respiratory complications of SjS include airway mucosal dryness, ILD, pleural thickening or effusion and non-Hodgkin lymphomas.

Airway Disease

The upper airway is often affected in SjS and a sensation of dryness of the nasal mucosa, mouth (xerostomia) and trachea (xerotrachea) are common. Small airway involvement and air trapping can be observed in the PFTs. Histopathology studies of lung tissue from patients with SjS with more severe obstructive lung disease have revealed evidence of lymphocytic or follicular bronchiolitis[42].

Interstitial Lung Disease

Clinically significant ILD is estimated to occur in 8% to 38% of patients with SjS[43]. The most common histopathologic pattern in SjS is nonspecific interstitial pneumonia. Other patterns including usual interstitial pneumonia and lymphocytic interstitial pneumonia were also noted[44]. The prognosis of nonspecific interstitial pneumonia, lymphocytic interstitial pneumonia, and organizing pneumonia in the setting of SjS is generally favorable[45]. Features associated with usual interstitial pneumonia, such as more extensive reticular changes on HRCT and a greater number of fibroblast foci on histologic examination, are associated with a worse prognosis.

Dermatomyositis/Polymyositis

Idiopathic inflammatory myopathies (IIM) are heterogeneous diseases of autoimmune origin that cause muscle weakness due to inflammation of the skeletal muscles. The main forms of IIM include polymyositis (PM), dermatomyositis (DM) and inclusion body myositis[46]. Both diseases are characterized by inflammatory muscle disease involving the proximal muscle groups, and DM is defined by its characteristic cutaneous involvement. Both are associated with underlying malignancy, with higher rates noted in DM[47]. Pulmonary complications of DM/PM are frequent, occurring in 40% of patients[48]. Manifestations include interstitial lung disease, aspiration pneumonia, and ventilator muscle weakness. A subset of PM/DM is the antisynthetase syndrome, which is characterized by a combination of clinical features that include inflammatory myopathy, ILD, fever, inflammatory arthritis, Raynaud phenomenon, mechanic's hands, and the presence of an anti–aminoacyl-tRNA–synthetase antibody[49].

Interstitial Lung Disease

ILD is the most common pulmonary complications of PM/DM, and is a major cause of morbidity and mortality. Abnormalities in the CT scan or PFTs may be present in 65% of patients with recently diagnosed PM/DM[50]. Women are more likely to develop ILD. The aminoacyl-tRNA-synthetase antibodies (Ab) are a predictive factor for development of interstitial disease[51]. The most common Ab is anti-histi-

dyl-tRNA-synthetase (anti-Jo-1 Ab), which is found in 20% of patients with myositis[52]. In a series of 90 patients with anti-Jo-1 antibodies, the incidence of ILD approached 90 percent[53]. By histopathologic studies, nonspecific interstitial pneumonia is the most common pattern seen on surgical lung biopsy followed by usual interstitial pneumonia and organizing pneumonia[54].

Summary

CTDs cause a myriad of pulmonary complications, including ILD, bronchiolitis, bronchiectasis, pleuritis, and pulmonary hypertension. ILD is a common and serious form of pulmonary involvement characterized by various patterns of inflammation and fibrosis on HRCT scan and in lung biopsy specimen. Although the various CTDs associated with ILD often are considered together because of their shared autoimmune nature, there are substantial differences in the clinical presentations and management of ILD in each specific CTD.

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結締組織疾病的肺部表徵

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摘　要

結締組織疾病患者若合併有肺臟侵犯，往往導致一定程度的併發症與死亡；而各種結締組織疾病患者或多或少都會波及肺臟、呼吸道或肋膜。乾咳、胸痛或呼吸困難，是最常見的症狀，而間質性肺病為最常見的表現。診斷上需排除感染或藥物相關毒性。肺功能檢查如一氧化碳瀰散試驗或是高解析胸部電腦斷層掃描，可以較早期地偵測肺臟疾病的存在。在放射影像模式和特發性間質性肺炎於病理結果的描述進展，現正應用到結締組織疾病的患者。治療取決於肺部病發症的類型，有些可能追蹤檢查即可；若病程惡化快速，甚至需要投與類固醇或免疫抑制藥物。