

Interstitial Lung Disease Manifestation of Connective Tissue Disease

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Abstract

Background: The connective tissue diseases (CTDs) are a group of systemic disorders characterized by autoimmune-mediated organ damage. Interstitial lung disease (ILD) represents a broad group of diffuse parenchymal lung injury patterns characterized by varying degrees of inflammation and fibrosis. In this review, we will highlight the clinical characteristics and management of the most common CTD-ILDs.

Data Sources: A review article of published articles between the year 1975 and 2017 were conducted using different electronic databases such as Pubmed, Medline, Google Scholar, Google Books, and from other cited websites. We used different key words to conduct the search like connective tissue disease; interstitial lung disease; CTD-ILD; Pneumonia; Respiratory failure and Rheumatoid arthritis (RA)

Conclusion: Interstitial lung disease (ILD) is one of the most serious pulmonary complications associated with connective tissue diseases (CTDs), resulting in significant morbidity and mortality. Early detection of ILD and a better understanding of factors that impact the progression of the disease may be helpful when making decisions regarding therapeutic interventions. Although several large randomized studies have examined the impact of immunosuppressive therapy for CTD-ILD, additional studies are needed to determine the optimal treatment strategies.

Keywords: *Connective Tissue Disease; Interstitial Lung Disease; CTD-ILD; Pneumonia; Systemic Sclerosis (SSc); Interstitial Lung Disease*

Introduction

Interstitial lung disease (ILD) is a group of disorders characterized by inflammation and scarring of the lung tissue [1]. Significant morbidity and shortened survival can be associated with connective tissue disease-associated interstitial lung disease (CTD-ILD). There are varieties of thoracic compartments that can be involved in each of the CTDs [2].

Clinical features of CTD-ILD

Pulmonary function test (PFT)

The PFT pattern in CTD-ILD usually show restrictive physiology and decreased diffusion capacity (DLco). Nevertheless, other patterns can be seen. Also, PFT usually elucidates the severity of the disease more accurately than chest radiography [3].

Histopathological patterns

The most common lung pattern among all CTD-ILD is non-specific interstitial pneumonia (NSIP) [4]. Only one exception, rheumatoid arthritis in which usual interstitial pneumonia (UIP) pattern pathology is more common [5]. It is observed that CTD-UIP has fewer

fibroblastic foci than CTD-associated idiopathic pulmonary fibrosis (CTD-IPF) [6]. Some studies demonstrate that the prognosis of CTD-UIP is better than CTD-NSIP although others show no difference in prognosis [7]. There are other patterns that are less commonly experienced such as diffuse alveolar damage (DAD), lymphocytic interstitial pneumonia (LIP), and desquamative interstitial pneumonia (DIP) [8]. There are discrepancies among clinicians about the use of surgical lung biopsy (SLBx) in the patients with CTD-ILD. Although many clinicians think that patients with CTD-UIP should undergo SLBx, others think that there is no need for it. The clinician that do not use it is either depending on pulmonary physiology in determining prognosis or thinking that there is no benefit of it for management and choice of treatment. These clinicians under the last category typically treat the disease with immunosuppressive medications. However, there is a consensus about the use of SLBx when there are other causes of ILD other than CTD such as malignancy or infection [9-11].

High-resolution computer tomography (HRCT) findings

HRCT scan provides detailed cross-sectional imaging of the lungs, which easily allow for identification of a variety of different interstitial lung diseases [12]. Even though each CTD exhibits a tendency to a certain pattern of parenchymal involvement, significant overlap exists. In general, a radiographic NSID pattern is observed most commonly in CTD-ILD and is described by intra-and interlobular reticular opacities in a predominantly subpleural and basilar distribution. Although it is demonstrated that Groundglass specificities may suggest that the disease is possible to be responsive to treatment, this is not always true. It is observed that reticulation, traction bronchiectasis, and honeycombing indicate fibrotic changes and more advanced ILD [13].

General strategies in management of CTD-ILD

Many forms of ILD can respond substantially to immunosuppressive therapies (IST) and corticosteroids (CST). However, ILD accompanied by extensive fibrosis may be difficult to treat. However, patients with idiopathic pulmonary fibrosis can benefit significantly from either supportive care (oxygen therapy, pulmonary rehabilitation) or lung transplantation. Unfortunately, only a relatively small subset of patients with end-stage ILD are able to meet wait listing requirements and eventually undergo successful lung transplantation [14].

ILD in specific CTD

Rheumatoid arthritis (RA)

RA is an autoimmune systemic disease that causes chronic inflammation of the joints and other organs in the body [15]. RA is different from osteoarthritis, common arthritis that often comes with older age [16]. It is observed that RA is three times more common in women than men [17]. It affects people of all races equally [18,19]. The disease can begin at any age and even affects children (juvenile idiopathic arthritis) [20]. However, it most often starts after 40 years of age and before 60 years of age [21]. The cause of RA is unknown. Although infectious agents such as viruses, bacteria, and fungi have long been suspected, none has been proven as the cause. It is believed that the tendency to develop rheumatoid arthritis may be genetically inherited (hereditary) [22,23]. Environmental factors also seem to play some role in causing RA. For example, scientists have reported that smoking tobacco, exposure to silica mineral, and chronic periodontal disease all increase the risk of developing rheumatoid arthritis [24,25].

RA-ILD is the most common pulmonary manifestation. Circulating autoantibodies, the most commonly being a rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), is associated with the development of ILD [26]. These antibodies can be present in the serum before any clinical manifestations [27]. Smoking has an essential role in RA-ILD by enhancing citrullination of lung proteins, so leading to the development of anti-CCP [28]. RA-ILD is hard to treat and has high morbidity rate [29]. It is recommended not to use drugs with high rates of pulmonary toxicity in RA patients with pre-existing lung disease because there are drugs that can induce ILD and worsen RA-ILD [30]. The website that lists all medications associated with pulmonary toxicity is pnemotox.com. Treatment for RA-ILD with disease-modifying antirheumatic drugs (DMARDs), including methotrexate, leflunomide, and azathioprine, as well as biologics, particularly tumor necrosis factor (TNF) inhibitors, have been typically used [31].

Patients in early stages can be helped with medications such as CST and IST and put on the waiting list for a lung transplant sooner. However, these treatments do not work for everyone. The best approach is to treat the underlying RA, even though ILD may get worse despite well-controlled RA [32].

Systemic sclerosis (SSc)

SSc (sometimes called scleroderma) is a significant devastating CTD characterized by multi-organ involvement, vasculopathy with endothelial dysfunction, and excessive collagen disposition [33,34]. Pulmonary disease in SSc consists of ILD and pulmonary arterial hypertension (PAH). SSc-ILD is the major cause of death in this disease along with PAH. It is noted that having ILD is much higher in patients with diffused cutaneous SSc than those with limited cutaneous SSc [35-37]. Although the exact pathways and mechanism of the pathogenesis of SSc-ILD is not clearly understood, three steps may be considered to be involved: 1) persistent and repeated bouts of injury to endothelial cells, 2) Activation of innate and adaptive immunity and 3) Fibroblast recruitment/activation, which leads to accumulation of extracellular matrix and scarring [35]. Transforming growth factor (TGF)- β play a substantial role in activation of several cascades pathways to enhance the disease progression [38]. Early treatment is mandatory because inflammation leads to fibrosis. The prevention of the disease progression is still more plausible and realistic goal than disease regression because there is no treatment that can reverse lung fibrosis. Non-selective immunosuppressors are still the most widely used treatment in SSc-ILD. Regarding of biological treatment, interesting results on the use of Rituximab (RTX) have been known. No anti-fibrotic drug shows a real efficacy in the prevention and treatment of fibrosis [35,39].

Polymyositis (PM)/Dermatomyositis (DM)

PM and DM are uncommon systemic rheumatic disorders characterized by inflammatory and degenerative changes in the muscle (polymyositis) or in the skin and muscle (dermatomyositis) [40]. The most specific skin signs are Gottron papules over the knuckles and a periorbital heliotropic rash [41,42]. The PD-ILD usually takes the form of NSIP. The disease can be present with rapid progression to respiratory failure or bronchiolitis obliterans organizing pneumonia (BOOP) [43]. Patients with PM/DM-ILD are at increased risk of malignancy, involving the lungs. So, it is essential to ascertain that the patient undergoes appropriate cancer screening [44]. Treatment recommendations are still limited by the absence of controlled trials and can be only based on experiences from small case series and case reports. At least some patients may get improved with IST, but data are limited, and longitudinal studies are needed [45]. Pulmonary disease exists in one- to two-thirds of the patients with PM/DM [46]. Diagnosis is investigated by clinical findings on muscle tests, which may include muscle enzymes, MRI, electromyography, and muscle biopsy [47]. Treatment usually includes Prednisone followed by IST [48].

Sjogren's syndrome (SS)

SS is an immune system disorder that can be accompanied by other immune system disorders such as RA and Lupus [49]. It is characterized by diminished lacrimal and salivary gland function and associated with lymphocytic infiltration of exocrine glands, especially the lacrimal and salivary glands [50]. Thus, it causes dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia) [51]. Also, SS can affect extra-glandular organs system including the skin, lungs, heart, kidney, neural, and hematopoietic systems [52]. SS is usually developed in people older than 40. However, it can be developed at any age as well. The disease is much more common in women [53]. When SS is associated with another CTD, it is referred to as primary SS. On the other hand, SS that is associated with CTD such as RA, lupus, or SSc, is referred to as secondary SS [54]. The most common manifestation of SS-ILD is NSIP in its fibrosing variant [55]. The main risk factor for the development of SS is being a member of a family that is already characterized as having an autoimmune illness. Thus, it is possible that certain genes that are inherited from ancestors can predispose one to the development of SS. However, SS can also be sporadic and occur in a person from a family with no known autoimmunity [56,57]. Patients with SS usually produce autoantibodies that can be detected through blood testing and include antinuclear antibodies (ANA). The autoantibodies that are typically found in most, but

not all patients, are SS-A and SS-B antibodies (also known as anti-rho and anti-La antibodies), rheumatoid factor, thyroid antibodies, and others [58]. Respiratory complications of SS include airway mucosal dryness (Xero trachea), a variety of ILDs, non-Hodgkin lymphomas, pleural thickening or effusion, and, rarely, thromboembolic disease or PH [59,60]. Actually, there is no cure for SS, and the treatment is directed toward the particular areas of the body that are involved to prevent complications [61].

Systemic Lupus Erythematosus (SLE)

SLE is an autoimmune heterogeneous disease that is characterized by the presence of autoantibodies directed against nuclear antigen. So, it is considered a multi-system disease [62]. SLE is more common in women than men and can occur at any age [63]. Nevertheless, most people that have the disease are between 15 and 44 [64]. It is also noted that the disease affects African Americans and Asians more often than people from other races [65,66]. The clinical manifestations vary from a person to another and may come and go. However, almost everyone with this disease has joint pain that can affect joints of fingers, hands, wrists, and knees. Some of these patients can develop arthritis. Other common symptoms are butterfly rash, difficulty breathing, fatigue, arrhythmias, fever with no causes, sensitivity to light, and mouth sores [67]. People that have only skin problems are called of having discoid lupus [68]. The patient can be diagnosed with the disease if the patient has 4 out of 11 common signs of this disease [69]. Usually, all people with lupus have a positive test for antinuclear antibody (ANA) but having positive ANA alone does not mean the person has lupus [70]. Autoantibodies can usually exist many years before the diagnosis of SLE [71]. Up to 50% of SLE patients will develop lung disease [72]. Even though pulmonary infections usually affect the airways and/or parenchyma, complications due to SLE may affect all compartments of the lungs and include pleuritis, ILD, alveolar hemorrhage, shrinking lung syndrome (SLS), PH, airways disease, and thromboembolism disease [73]. Acute lupus pneumonitis (ALP) is uncommon but a well-recognized manifestation of SLE, that can be difficult to be characterized from infectious pneumonia [74]. The histopathological findings of SLE-ILD can show interstitial lymphocytic infiltrates with prominent lymphoid nodules [75]. The goal of treatment is to control symptoms as there is no cure for SLE. Mild forms of the disease can be treated by NSAIDs, CST, and IST [76].

Mixed connective tissue disease (MCTD)

MCTD is an overlap disease that has overlapping signs and symptoms of a combination of disorders, primarily SLE, SSc, and PM/DM. It is characterized by the presence of a distinctive antibody against U1-ribonucleoprotein (RNP) which can precede overt clinical manifestations of MCTD [77,78]. The clinical features of MCTD include Raynaud phenomenon, swollen hands, arthritis, arcus sclerosis, esophageal dysmotility, lung fibrosis, PH, myositis, high level of anti-U1-RNP antibodies, and antibodies against U1-70 kd small nuclear ribonucleoprotein (SnRNP) [79,80]. Immunoglobulin G (IgG) anticardiolipin antibodies are a marker for the development of PH which is the most common disease-related cause of death [81]. MCTD has been reported in all races [82]. The female-to-male ratio of MCTD is approximately 3:1 [83]. The onset of the disease is usually at 15 - 25 years of age, but can occur at any age [84]. The overall therapy is to treat of symptoms and to monitor of complications, such as PH [85].

Conclusion

CTD-ILD comprises a heterogeneous group of disorders characterized by different degrees of fibrosis and/or inflammation within the lung parenchyma. Rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD) can all be associated with the development of ILD. Non-specific interstitial pneumonia (NSIP) is the most commonly observed histopathological pattern in CTD-ILD. However, other patterns including usual interstitial pneumonia (UIP), organizing pneumonia (OP), diffuse alveolar damage (DAD) and lymphocytic interstitial pneumonia (LIP) may occur. The usual treatment of CTD-ILD is focused on relieving symptoms and prevention of disease progression. Typically, immunosuppressive therapy (IST) and corticosteroids (CST) are used for this approach. In this review, we highlighted the significant aspects of CTD-ILDs. 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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