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Interstitial Lung Disease in Scleroderma: Clinical Features and Pathogenesis

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Abstract

Interstitial lung disease is a prevalent but worrisome implication in scleroderma. It is now the leading cause of morbidity and mortality since the dramatic reduction in death caused by scleroderma renal crisis. However, the pathogenesis remains unknown. Most observers suggest that lung injury induces microvascular damage and immunologically-mediated inflammation. As oxidative stress and leukotrienes-lipoxins imbalance is observed in -ILD patients, a series of proinflammatory and profibrotic cytokines are also found. Possible biomarkers including SP-D, KL-6, Caveolin-1, IL-6, IL-1 may be useful index for diagnosis and progression, which also suggest the potential mechanism. There are also some studies focusing the relationship between gastroesophageal reflux (GER) and SSc-ILD, which partly explain the mechanism from a new perspective.

Keywords: Systemic sclerosis; Interstitial lung disease; Clinical features; Pathogenesis

Introduction

Scleroderma (systemic sclerosis, SSc) is an autoimmune disease charactered by disease-specific autoantibodis, vasculopathy and progressive fibrosis in skin and internal organs [1]. Though SSc pathogenesis remains unclear, it's accepted that both genetics and environmental factors contribute to disease susceptibility, clinical presentation and progression [2]. According to the maximum extent of skin involvement, SSc is widely classified into two subtypes: limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) [3]. Nowadays, the mortality of SSc has decreased, but it is stilldevastating and worrisome.

The internal organs involvement range from lung, gastrointestinal tract, kidney, musculoskeletal system and heart. Lung involvement in SSc occurs more frequently than in other connective tissue diseases, which includes interstitial lung disease (ILD), pulmonary vascular disease, chronic aspiration airway disease, neuromuscular weakness, extrinsic pulmonary restrictive pathology, pleural effusions, pneumothorax and lung cancer [4]. In a recent cohort study, it's proved that lung involvement contributes to 23% of SSc death, just following heart involvement (29%) [5]. However, among these pulmonary complications, ILD is the most prevalent and troublesome one.

ILD represents a heterogenous group of noninfectious, acute or chronic, diffuse parenchymal lung disorders. It is defined as chest radiograph evidence of bilateral, diffuse parenchymal opacities (reticular, interstitial subsegmental opa-cties) in an apparently normal host [6]. It is reported to exist in nearly 60% of SSc patients with clinical involvement and approximately 80% of SSc patients at autopsy. Though only 15% of SSc-ILD patients (usually dcSSc) progress to severe restrictive lung disease, its mortality is still threatening accounting for nearly 33% of SSc death [7,8]. It is now the leading cause of morbidity and mortality since the dramatic reduction in death caused by scleroderma renal crisis.

Though the survival in patients with SSc-ILD is reported to be better than in patients with other CTD-ILD, its most popularity and highest case-specific mortality is still worrying [9]. In patients with scleroderma, ILD predicts increased mortality. The majority of SSc-ILD patients show replacement of the normal lung parenchyma with inflamed and fibrotic tissue, which is ineffective for gas exchange [10].

Up to 42% of SSc-ILD patients will die of disease progression within 10 years of diagnosis [11]. It was also illustrated by a retrospective study of 953 patients with SSc. They found that patients with severe ILD had a nine-year survival rate of approximately 30 percent, whereas patients with SSc who did not have severe involvement of an organ system had a nine-year survival rate of 72 percent [12].

The risk of progression of SSc-ILD is the highest in the first 4 years of systemic disease, and especially in the first 2 years and in a small subset of patients in whom lung disease precedes the cutaneous manifestations of SSc.

These days, the choices for treatment are increasing, but the treatment effects are not satisfying. Treatment with cyclophosphamide or lymphocyte modulating agents shows a modest benefit in delaying disease progression. The prevalence of gastroesophageal reflux disease and ongoing autoimmunity in these patients frequently leads to poor outcomes following lung transplantation.

Considering the severity of this disease, more intention is fueled and some achievements have been made. In this review, we mainly focus the clinical features, especially the new insights in the pathogenesis of SSc-ILD.

Clinical Features and Diagnosis

SSc-ILD is known as a rare and potentially lethal and devastating autoimmune disease. The two main complaints in SSc-ILD patient are usually dyspnea on exertion and nonproductive cough. However, these presentations often occur at a late stage. On physical examination, the most common abnormality is the presence of bi-basilar dry "velcro" crackles at lung bases.As dyspnea is the main manifestation, SSc-ILD should be differentiated from pulmonary hypertension, myocardial involvement, deconditioning, aspiration pneumonitis, interstitial pulmonary fibrosis and idiopathic ILD [13].

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Up to now, there is no definite standard diagnostic criteria. The diagnosis relies on chest high resolution computed tomography (HRCT), pulmonary function testing, Bronchoalveolar lavage (BAL) fluid analysis and lung biopsy. In a case reported by Kristine Phillips, the patient was mainly diagnosed by HRCT, pulmonary function testing and lung biopsy [14]. The characteristics of clinical features are presented as Table 1.

Conventional chest radiography can show linear shadow, even a "honey comb" reticular appearance at the periphery of the lung at the bases. More effectively, HRCT abnormalities have been shown in nearly 90% of SSc-ILD patients similar to that found at autopsy. These abnormalities include ground glass (a evidence of alveolitis), sub-pleural lines, honeycombing and parenchymal bands (symptoms of irreversible pulmonary fibrosis) [15]. Pulmonary function testing often reveal a restrictive ventilatory defect with a reduction in total lung capacity (TLC), vital capacity (VC), forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO).

BAL fluid from SSc-ILD patients has been investigated with an increased percentage of neutrophils, eosinophils and lymphocytes, often referred to as "alveolitis". This kind of alveolitis not only prove active lung disease in scleroderma, but also has prognostic value. BAL cells also express a large spectrum of factors from cytokines, chemokines, growth factors to coagulation factors, which to some extent explain the inflammation and fibrosis at autopsy [16].

Histopathologically, the autopsy in majority is characterized by a pattern termed as nonspecific interstitial pneumonia (NSIP): varying degrees of pulmonary inflammation and fibrosis. The early stage being primarily inflammatory is commonly termed as cellular NSIP, while others being primarily fibrotic known as fibrotic NSIP. The minority of SSc-ILD patients show a pattern of usual interstitial pneumonia (UIP) characterized by a nonuniform distribution of alternating zones of dense fibrosis, fibroblast foci, scant inflammation, normal lung and honeycomb change [17].

What is more, in the recent review written by A Tan, he summarizes the advancing diagnostic indexes or tools include exhaled nitric oxide, HRCT, computer-aided diagnosis (CAD) software and staging algorithm [18]. As more intense search has been fueled, a early and accurate diagnosis is expecting.

New Insights in Pathogenesis

The pathogenesis of SSc-ILD remains unclear. The BAL analysis and autopsy suggests that the two main characteristics of SSc-ILD are excessive fibrosis and inflammatory cell infiltration. Though the definite mechanism is still unknown, the current consensus supports the microvascular injury and the immunologically-mediated inflammatory theories. Then these factors probably act together to induce pulmonary fibrosis. Endothelial lesions, activation of coagulation proteases, especially thrombin, fibroblast proliferation, and differentiation of normal lung fibroblasts to a myofibroblasts phenotype are hallmarks of ILD in SSc. There are also some studies focusing the relationship between gastroesophageal reflux (GER) and SSc-ILD, which partly explain the mechanism from a new perspective.

Main complaints	**worsening dyspnea**
Physical examination	**the presence of bi-basilar crackles**
lung biopsy	**the presence of NSIP**
HRCT	**the presence of bilateral infiltrates in the lower lobes**
Pulmonary function	**a reduction in FVC and DLCO**

Table 1: Clinical features of the patient.

Microvascular injury

The earliest phase of SSc-ILD is characterized by microvascular injury and alveolitis. Just like Raynaud's phenomenon precedes the onset of skin fibrosis, vascular damage precedes evidence of fibrosis in histology. Though the sequence of events and interplay with autoimmunity is not at all clear. It has been suggested that microvascular injury induces inflammation and autoimmunity, which in turn has direct or indirect roles in stimulating fibroblast activation, a key event in the development of fibrosis [19]. This process may correlate with chemokines endothelin-1 (ET-1), thrombin, ß thromboglobulin and platelet factor 4, which can reflect vascular damage.

Abraham et al. reported an expression of ET-1 on SSc-ILD patients' interstitial vessels. At the same time, an overall increase in ET receptor existed [20]. ET-1, known as a vasoconstrictor and mitogenic peptide, can induce fibrosis directly by binding to ETA and ETB receptors on fibroblasts, or indirectly by inducing fibrogenic cytokines such as transforming growth factor (TGF-ß) [21]. On the one hand, ET-1 can induce epithelial–mesenchymal transition (EMT) via ETA activation. On the other hand, ET-1 can induce expression of alpha-smooth muscle actin (a-SMA) and other proteins that contribute to the contractile phenotype of myofibroblasts.

Thrombin is a multifunctional serine protease and a key enzyme of blood coagulation that catalyzes the conversion of fibrinogen to fibrin [22]. In SSc-ILD patients, higher thrombin activity is significantly observed in BALF and lung tissue. It is observed that thrombin can induce apoptosis in alveolar epithelial cells by cleaving caspase-3 and increasing DNA fragments, can differentiate lung fibroblasts to a profibrotic myofibroblast phenotype resistant to apoptosis by inducing a higher expression of α-SMA and by rapid phosphorylation of Akt [23]. Anna Ludwicka-Bradley et al. concluded that thrombin could activate pathogenic Th2 lymphocyte profile, modulate tissue repair responses, stimulate transformation of epithelial cells, endothelial cells, fibroblasts into myofibroblast phenotype and induces secretion of several proimmune and profibrotic factors, which serve as antigens for pathogenic autoantibodies production in SSc-ILD [24].

Compare with ET-1 and thrombin, B thromboglobulin (BTG) and platelet factor 4 (PF4) seem less important. BTG and PF4 are platelet activation markers, which are released from activated platelets and considered to be the markers of platelet activation [25]. Microvascular injury lead to chronic platelet activation, while activated platelets may play a role in inflammation through release of chemotactic factors and production of proinflammatory eicosanoids [26].

Oxidative stress and leukotrienes-lipoxins imbalance

8-isoprostane is a biomarker of oxidative stress produced primarily by free radical-induced peroxidation of arachidonic acid. A high serum level of 8-isoprostane is reported to exist in 99% of SSc patients [27]. Increased 8-isoprostane levels correlated with the severity of both renal vascular damage and lung fibrosis. In Ellen Tufvesson's study, they found that 8-isoprostane and leukotrienes (LTs) were increased in exhaled breath condensate (EBC) in SSc patients than that in controls. It reflects the inflammatory pattern in SSc involving LTs as well as oxidative stress [28]. LTs are potent proinflammatory mediators and directly or indirectly stimulate fibroblast chemotaxis, proliferation, and collagen synthesis. Simultaneously, lipoxins, a anti-inflammatory and antifibrotic agent, can counter-regulate the proinflammatory actions of leukotrienes, activate resolution of the inflammatory response and inhibit growth-factor-induced fibroblast proliferation and collagen synthesis. Though lipoxins are also overproduced in BAL, they cannot

Cytokines	Function
TGF-ß	Consistent stimulating effects on extracellular matrix production Regulation of fibroblast proliferation
CTGF	A active stimulant of collagen and fibronectin production Increase the transcription of type I collagen
PDGF	Stimulate the production of extracellular matrix components Stimulate autocrine production of a profibrotic chemokine, MCP-1
OSM	Stimulates proliferation of fibroblasts Production of collagen and glycosaminoglycan
Interleukin-4	Stimulate fibroblast proliferation Produce collagen, chemotaxis, expression of adhesion molecules ICAM-1 and VCAM-1
IFN-γ	Inhibit fibroblast proliferation and production of collagen
MCP-1	Upregulates production of collagen through autocrine TGF- β
PARC	Stimulate collagen mRNA and protein production through activation of transcription factors Sp1 and c-Myb

Potential cellular sources of the profibrotic cytokines and chemokines in scleroderma lung disease include alternatively activated macrophages, activated CD8+T cells, eosinophils, mast cells, epithelial cells and fibroblasts themselves.

Table 2: Proinflammatory and profibrotic cytokines.

balance the proinflammatory and profibrotic effects of LTs [29]. These findings may indicate a potential value for assessment of disease progress and therapy evaluation in SSc-ILD patients [30-32].

Proinflammatory and profibrotic cytokines

Increased amounts of mRNA or protein for multiple profibrotic cytokines and chemokines have been identified in lung tissue and broncholveolar lavage samples from scleroderma patients. These cytokines range from TGF-ß, connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), oncostatin M (OSM), monocyte chemotactic protein-1 (MCP-1) to pulmonary and activation-regulated chemokine (PARC). In Sergei P. Atamas' investigation, a larger spectrum of cytokines and chemokines is observed [33].

Autoimmunity

SSc-ILD is an autoimmune disease associated with lymphocyte activation and release of various cytokines and growth factors. It is also characterized with a marvelous number of autoantibodies, which can cause vascular and tissue injury then amplify the immune response.

Immune cell abnormalities

Lymphoid follicles can be seen at autopsy, which suggests that T lymphocytes may play an important role in the development SSc-ILD. In a study made by Boin F, 62 patients were compared by flow cytometry, they found that SSc-ILD patients had a marked reduction of CCR5 (Th1/Tc1-specific chemokine receptor) /CRTH2 T cell ratios [34]. It partly explains why Th2 type cytokines are more secreted (Th2 dominance hypothesis). However, G. N. Andersen not only found an increased production of Th2 cytokines (IL-4,IL-5,IL-6) in SSc patients alveolar and peripheral blood T lymphocytes, but also they found that Th1 cytokines (Interferon-gamma ,IFN-γ) were significantly increased in both, which is more significant in peripheral blood than alveolar T lymphocytes [35]. The author suggests a mixed Th1 / Th2 cytokine response in SSc-ILD. At the same time, it may be another evidence for the conclusion that Th1 activation occurs mainly in the peripheral blood of SSc patients. Moreover, Th2 cytokines can stimulate fibroblasts to overproduce collagen and other connective tissue matrix proteins. While IL-4 can stimulate fibroblast proliferation and increase collagen synthesis, IL-6 can assist IL-4 inducing Th2 differentiation, stimulate B-cell activation and fibroblast collagen and glycosaminglycan synthesis by inhibiting the Th1 reaction through the suppression of IFN-γ signaling [36]. Obviously, these cytokines may significantly contribute to the fibrosis in SSc-ILD.

Not only T lymphocytes, but also B lymphocytes were reported to exist in SSc-ILD biopsies. The presence of B cell infiltration suggests that these cells may contribute to disease pathogenesis [37]. CD19 expression correlated with the number of B-cells in the bronchoalveolar lavage fluid. Ye Gan et al. found that CD19 cells expressed semaphorin7A, then they further proved that semaphorin7A promotes TGF-beta1 inducing the accumulation of fibrocytes, contributing to inflammation and fibrosis [38]. It may suggest a relationship between B lymphocytes and fibrocyte biology in fibrogenic disorders. Moreover, CD19 deficiency inhibits the accumulation of B-cells in the alveolar compartment following BLM challenge. In animal model, the investigators reported that BLM administration to CD19 knockout mice led to attenuation of BLM-induced lung fibrosis [39]. Though the potential role of B-cells in SSc-ILD has been inadequately investigated, B cell deletion therapy is a new hope for patients.

Autoantibodies

Patients with systemic sclerosis express a variety of disease-specific autoantibodies, mainly including anti-topoisomerase (ATA, also known as Scl-70), anti-centromere (ACA) and anti RNA polymerase I/III (ARA). Besides, anti-Th/To, anti-U3RNP and anti-PM/Scl autoantibodies are less popular specific autoantibodies, while nonspecific autoantibodies include anti-Ro (SS-A) and anti-La (SS-B) [40]. Most (90%) patients with SSc show anti-nuclear antibodies. Among antibodies specific to SSc, anti-topoisomerase 1 antibodies found in 20%–40% of patients, which are more often present in dcSSc associated with ILD, whereas anti-centromere antibodies are more often associated with lcSSc and are rarely present with ILD. Anti-Th/Tho antibodies are nuclear antibodies which occur in lcSSc associated with ILD [41]. Besides, Wang Qian tested 62 SSc patients' serum by enzyme linked immunosorbent assay (ELISA), then came to a conclusion that anti-moesin antibody had comparatively high specificity for SSc-associated ILD patients. It contributes to further understanding the pathogenesis of ILD in SSc patients [42].

The types of the spectrum of autoantibodies may be treated as a diagnotic and predictive tool. Other autoantibodies associated with SSc-ILD, especially antiendothelial cell antibodies, antifibroblast antibodies, antiphospholipid antibodies, antibodies to Matrix Metalloproteinases (MMPs) and antibodies to PDGR receptors are receiving more attention. However, the mechanism of these autoantibodies in SSc-ILD remains unclear.

Possible biomarks

In healthy people, the majority (98%) of BAL cells are alveolar macrophages. However, in SSc-ILD patients, a prominent increased percent of neutrophils, eosinophils lymphocytes is largely observed. Some studies referred lung injury as the initial change. In response, bronchiolar epithelial and alveolar cells produce and secrete more SP-D, which is a member of collagenase subfamily of collectin, participating in a range of innate immune and inflammatory responses [43,44]. In the same way, the biomarker KL-6, a human MUC1 mucin secreted by type II pneumocytes, is over produced. Nowadays, its value for di-

agnosis and prognosis is hotly studied. In Faye N. Hant's review, they observed that recombinant KL-6 can significantly increase the rate of migration of lung fibroblasts into the wounded area in both a dose- and time-dependent manner compared with controls, supporting the potential of KL-6 in lung tissue repair and fibrosis [45]. KL-6 may actually play a role in the process of lung fibrosis through its chemotactic effects on migration of lung fibroblasts. Recently, it is reported that KL-6 shows a stronger association with decreased DLCO, decreased FVC and disease activity than SP-D [46]. More evidence is expected to clarify the status of these two biomarkers in SSc-ILD.

Caveolin-1 is the main component of the caveolae plasma membranes found in most cell types. The protein links integrin subunits to the tyrosine kinase FYN, an initiating step in coupling integrins to the Ras-ERK pathway and promoting cell cycle progression. It is also observed that it can regulate TGF-ß /Smad signaling through an interaction with the TGF-ß type I receptor, and interact with tyrosine phosphorylation to regulate endothelial nitric oxide synthase [47]; while these factors are relatively related with SSc-ILD. Moreover, in SSc patients' lung fibroblasts and in the lungs of bleomycin-treated mice, reduced levels of caveolin-1 are observed and they can promote collagen overexpression and lung fibrosis. In PBMC from bleomycin-treated mice, caveolin-1 expression was reduced by more than 50% and CXCR4 expression was increased by more than 40%. They found a massive increase in CXCR4 and its ligand CXCL12 in the lung tissues of SSC-ILD patients. In PBMC, nearly 60 % less caveolin-1 and three times as much CXCR4 as their normal counterparts. The overexpression of systemic administration of the synthetic caveolin-1 scaffolding domain (CSD) peptide one day prior to bleomycin almost completely blocked monocyte accumulation in lung tissue. TGF-β increased monocyte migration, but migration was inhibited > 80 % by CSD peptide. In summary, CSD peptide to compensate for low caveolin-1 levels may be a useful treatment strategy for SSc and other inflammatory/fibrotic lung diseases [48].

IL-16 is an immunoregulatory cytokine produced by leukocytes, epithelial cells, and fibroblasts and is present in lungs of patients with a variety of inflammatory lung diseases. It can represent a marker of fibroblast or epithelial cell activity in active SSc-ILD and contribute to the dominance of Th-1 cells which could be mediating chronic inflammation. It is observed that patients with low BAL IL-16 levels are less likely to have active SSc-ILD but those who do have a longer remission with CYC than patients with higher concentrations. IL-16 levels in BAL may be useful in identifying patients with SSc-ILD who would benefit from treatment with CYC [49].

Increased concentrations of interleukin-1 (IL-1) were observed in bronchoalveolar lavage fluids from patients with scleroderma and their levels were correlated with he patients' forced vital capacity (FVC). It is observed that the IL-1betaC+ 3962T SNP is associated with the presence of severe restrictive lung physiology in Italian SSc patients [50].

Gastroesophageal reflux (GER)

The definite relationship between GER and SSc-ILD is obscure. In a study made by RomyB.Christmann, they observed a positive relationship not only in Clinic presentation and radiology, but also in histopathology through the last 20 years'achievement made by scleroderma observers [51]. Presence of severe esophageal motor impairment was found to be associated with significantly decreased values of DLCO and evidence of ILD by HRCT. Furthermore, a 2 year follow-up suggested that patients with severe esophageal dysmotility had greater deterioration in DLCO and increased frequency of ILD by HRCT [52].

Conclusion

ILD in scleroderma is a group of lung diseases affecting the interstitium alveolar epithelium, pulmonary capillary endothelium, basement membrane, perivascular and perilymphatic tissues. Though the mechanism remains unknown, some achievements have been made. It's widely accepted as a disease charactered by inflammatory reaction and immune abnormalities. Nowadays, new biomarkers including SP-D, KL-6, Caveolin-1, IL-6, IL-1 are illustrated to play an potential role in the pathogenesis of SSc-ILD, while they are commonly received as prognostic index. We expect further study towards the expand system of immunologic and molecular change in SSc-ILD patients to find a efficient way to prevent or improve the condition of lung tissue fibrosis.

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