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Update on scleroderma-associated interstitial lung disease

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Abstract

Systemic sclerosis (SSc), or scleroderma, is a heterogeneous and complex autoimmune disease characterized by varying degrees of skin and organ fibrosis and obliterative vasculopathy. The disease results in significant morbidity and mortality and to date available treatments are limited. Lung involvement is currently the leading cause of death of patients with SSc. Over the past year, significant advances have been made in our understanding of SSc-associated lung disease and this review attempts to encapsulate these most recent findings and place them in context. We divide our discussion of the most recent literature into 1) clinical aspects of SSc lung management, including classification, imaging, biomarkers, and treatment; 2) promising new animal models that may improve our ability to accurately study this disease; and 3) studies that advance or change our understanding of lung disease pathogenesis, thereby raising the potential for new targets for therapeutic intervention. The goal of this review is to highlight and summarize the most significant studies of the past year and to bring clinicians and researchers alike in the field up to date.

Keywords

Systemic sclerosis/scleroderma; lung fibrosis; autoimmune; connective tissue disease; interstitial lung disease

Introduction

Systemic sclerosis (SSc), or scleroderma, is a clinically heterogeneous, autoimmune disease characterized by fibrosis of skin and visceral organs as well as obliterative vasculopathy. The disease is one of considerable morbidity and mortality. Roughly 70% of patients develop pulmonary complications of interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) and in recent years SSc-associated lung disease has become the leading cause of death in scleroderma patients(1). One major challenge in this disease is the broad spectrum of phenotypic presentations, laboratory and serologic findings, responses to treatment, and clinical outcomes among patients(2). The heterogeneous nature of the disease presents a significant challenge to investigators seeking to understand its pathogenesis and develop therapies that will be uniformly effective. In this review, we highlight the latest developments in the field of scleroderma lung disease and discuss their implications.

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Clinical Aspects

The heterogeneity of the scleroderma patient population in clinical presentation, response to treatment, and disease progression underscores the importance of accurately evaluating and grouping patients according to phenotype. The most widely-used approach set forth by LeRoy *et al.*(3) in 1988 divides patients based upon their degree of skin involvement into limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) subsets. Although this classification system has withstood the test of time, some patients do not fit well into either group. These include patients with scleroderma overlap (SSc-overlap) syndrome, who share features of their disease with another connective tissue disease (CTD). In a comprehensive German study, Moinzadeh *et al.*(4) followed 342 SSc-overlap patients for a mean of 9.5 years. These patients presented earlier and manifested a similar degree of skin involvement as lcSSc patients. Their rate of progression of pulmonary and renal complications was intermediate to lcSSc and dcSSc patients. Musculoskeletal complications were increased in SSc-overlap patients compared to patients with either lcSSc or dcSSc disease. This study represents one of the largest cohorts of SSc-overlap patients studied to date and outlines why these patients should be considered a distinct subset of SSc.

Given the chronic nature of the disease, it is paramount that clinicians and researchers determine how best to follow patients with SSc longterm and detect complications such as ILD and PAH early. McCall *et al.*(5) studied SSc patients who underwent chest CT imaging and right heart catheterization (RHC) within six months of each other. In patients with forced vital capacity (FVC) ≥70%, a main pulmonary artery diameter (MPAD) ≥30mm correlated strongly with the presence of pulmonary hypertension on RHC. Thus, in patients with FVC≥70%, the MPAD may be a valuable screening test to determine whether more invasive testing to evaluate for pulmonary hypertension is needed. Mohammadi *et al.*(6*) compared a modified lung ultrasonography examination to the gold standard high resolution chest CT (HRCT) in the detection of SSc-associated ILD. The ultrasound beam reflects off of thickened subpleural interlobular septa, generating B-line artifacts that were quantified in a total of 10 designated intercostal spaces. Findings from this modified ultrasound protocol correlated well with those on HRCT. Ultrasound is fast, minimally invasive, and without risk of accumulative radiation exposure.

Several recent papers identified biomarkers that correlate with the severity of fibrosis in SSc. Elevated circulating levels of lysyl oxidase (LOX)(7); chitinase 1(8); tenascin-C (TN-C)(9); growth factor binding protein-15 (GDF-15)(10); cartilage oligomeric matrix protein (COMP or thrombospondin-5)(11); the epithelial cell antigen, Krebs vonden Lungen-6 (KL-6)(11); and the chemokine, CXCL4(12**), all correlate with the presence of SSc-associated ILD. Elevated BAL levels of the chemokines, CXCL5 and CXCL8, as well as the damage associated molecular pattern molecule, S100A8/A9, also correlated with greater evidence of fibrosis on HRCT(11). Serum IL-6 predicted early disease progression and risk of death within the first 30 months in patients with mild SSc-associated ILD(13).

A recent large study from the Canadian Scleroderma Research Group confirmed the link between esophageal involvement and SSc-associated ILD. Zhang *et al.*(14) identified that symptoms of esophageal dysmotility and GERD were associated with declining FVC and

progressive restrictive lung disease in patients with SSc. This is presumably due to silent aspiration causing lung injury and scarring. The European Scleroderma Trial and Research (EUSTAR) group published promising results from the first multicenter nested case-controlled study of rituximab in SSc(15**). They found significant reduction in skin fibrosis in the rituximab-treated patients and also stabilization of SSc-associated ILD at 6 months follow-up. The side effect profile of the drug appeared acceptable and no serious adverse events were reported.

Saketkoo *et al*.(16**) summarized the proceedings of the Connective Tissue Disease Interstitial Lung Disease (CTD-ILD) Working Group during the Outcome Measures in Rheumatology 11 (OMERACT 11) conference. The CTD-ILD Working Group recognizes the need for consensus regarding validated outcome measures to gauge efficacy of new ILD therapies in clinical trials. Both clinicians and researchers with expertise in CTD-ILD and those focused on idiopathic pulmonary fibrosis (IPF) joined forces in an important, concerted group effort to devise common goals for the treatment of ILD, whether idiopathic or associated with rheumatologic disease. In addition, SSc patients were asked for direct input and the group made a firm commitment to place more weight on the patient experience. Two patient-centered symptoms (ie. cough and dyspnea) were adopted as well as quality of life indices as meaningful outcome measures in future clinical trials.

De Cruz *et al*.(17) discussed the UCLA lung transplantation experience in scleroderma. Querying the United Network for Organ Sharing (UNOS) database reveals that only 196 of 25,260 lung transplants (0.7%) performed in the United States for end-stage lung disease from January 1988 to January 2013 were done in patients with SSc. Barriers to candidacy for lung transplantation in SSc include severe skin breakdown raising the risk of post-transplant infection, renal dysfunction, severe esophageal dysmotility and gastroparesis despite maximal medical therapy, and significant cardiac conduction abnormalities. The authors make the point that lung transplantation remains a viable option in a carefully-selected group of SSc patients.

Animal Models

While they have limitations, animal models of lung fibrosis are invaluable and required to test potential new therapies prior to their use in humans. Two recent papers add mouse models of particular relevance to scleroderma to the experimental repertoire. Lee *et al*.(18) compared the commonly used single intraoral bleomycin dose model with continuous systemic delivery of bleomycin via subcutaneous osmotic minipump infusion. Not only did the mice experience less weight loss and improved survival in the pump model, but they also developed disease that more closely replicated human SSc. These mice had subpleural lung involvement, only limited inflammation, induction of a hypertrophic type II alveolar epithelial cell population, and skin in addition to lung fibrosis. Manetti *et al*(19) found that uPAR-deficient mice developed progressive lung and skin fibrosis and peripheral microvasculopathy over time. This study is important not only because these mice can be used to more effectively model human SSc, but also because it suggests a central role for uPAR in the pathogenesis of the disease.

Pathogenesis

This section touches on many articles which provide clues to different pathways and mechanisms potentially involved in fibrogenesis in scleroderma.

Originally identified as the lipopolysaccharide (LPS) receptor, TLR4 is widely recognized as central to innate immune responses to gram-negative bacteria. TLR4, however, can also be activated by endogenous ligands generated by cellular injury, ECM remodeling, autoimmune responses, and oxidative stress. Bhattacharyya *et al.(*20*) demonstrated increased TLR4 expression in skin and lung biopsy specimens and primary skin fibroblasts isolated from SSc patients. Tissue staining for potential endogenous ligands for TLR4 was also increased. TLR4 activation potentiated canonical TGF-β signaling and suppressed anti-fibrotic microRNA. This study establishes the importance of the TLR4 axis in scleroderma. A related paper from the same group suggests that increased levels of the endogenous damage-induced TLR4 ligand, fibronectin extra domain A(Fn^{EDA}), may be responsible for sustained TLR4 activation and fibrogenesis in scleroderma(21).

Thrombin levels are increased in BAL from patients with SSc and in the bleomycin lung fibrosis model(22, 23). Thrombin, a serine protease with pleiotropic effects, induces profibrotic cytokines, growth factors, and extracellular matrix production and promotes the myofibroblast phenotype and alveolar epithelial cell (AEC) apoptosis(24). Atanelishvili *et al.*(25) demonstrated differential effects of thrombin on AECs vs. lung fibroblasts. Thrombin selectively up-regulates CCAAT enhancer-binding homologous protein (CHOP), a pro-apoptotic transcription factor, in AECs, predisposing them to apoptosis, while simultaneously down-regulating CHOP in lung fibroblasts, making them more resistant to apoptosis.

This past year several genetic studies were published on scleroderma. Lindahl *et al*(26) performed gene expression profiling of primary lung fibroblasts cultured from patients with SSc-associated ILD, IPF, and controls. The TGF-β response signature was upregulated while interferon-stimulated genes were suppressed in the SSc fibroblast. These findings are in contrast to those of Christmann *et al(*27*). Their microarray analysis of lung biopsies from SSc patients linked upregulation of TGF-β- and interferon-regulated genes as well as genes involved in macrophage activation with progressive SSc-ILD. These two studies follow one by Hsu *et al.*(28) in which signatures from lung tissues of SSc and IPF patients were compared to signatures of matching primary fibroblasts.

Assassi *et al.*(29) conducted gene expression arrays on skin biopsy samples from 59 SSc patients and identified 82 skin transcripts that correlated with severity of SSc-ILD. Plasma levels of two proteins encoded by these genes, CCL2 and soluble P-selectin glycoprotein ligand 1 (sPSGL-1), correlated with FVC values, thus showing potential as biomarkers for SSc-ILD. Finally, two papers out of Europe independently determined that a polymorphism on the MUC5B promoter (rs35705950) associated with IPF has no association with SSc(30, 31).

Elevated levels of circulating interleukin-33 in patients with SSc have been reported to correlate with severity of skin fibrosis and ILD(32). Luzina *et al.*(33) report that IL-33

potentiates bleomycin-induced lung injury and fibrosis in mice using an adenovirus overexpression system. In this setting, they found significantly increased levels of total (but not active) TGF-β, MCP-1, MIP-1, IL-6, and TNF-α in lung homogenates from mice treated with bleomycin plus intratracheal adenovirus expressing full-length IL-33 compared to mice receiving bleomycin alone. Heat shock protein-70 (HSP-70) was also increased in these mice.

Caveolin-1 curtails TGF-β signaling in fibroblasts by inhibiting smad 3 phosphorylation(34) and increasing the endocytosis and degradation of TGF-β ligand-receptor complexes(35–37). Reese *et al.(*38*) examined monocytes from healthy African American donors and found that they resembled monocytes from patients with established SSc, with low levels of surface caveolin-1, enhanced migration in response to chemotactic signals, and accelerated differentiation into fibrocytes. The authors propose that these pre-clinical monocyte changes may explain why African Americans tend to develop more severe forms of SSc, including SSc-ILD (38). More recently, reduced cav-1 levels in sputum were found to be associated with SSc-ILD(39).

Two papers from a group in Italy examined the antifibrotic effects of the small ubiquitous protein, thymosin β4 (Tβ4), in the bleomycin model. High levels of Tβ4 have been detected in the BAL fluid of patients with SSc-associated ILD, with lower BAL fluid levels of the protein correlating with risk of disease progression(40). This protein has multiple biologic effects, promoting cell motility and cell adhesion, inhibiting apoptosis, and down-regulating inflammation(41). A peptide derived from its aminoterminal end, Ac-sdkp, is responsible for the antifibrotic effects of angiotensin converting enzyme inhibitors(42). Conte *et al.*(43) found that exogenous Tβ4 is protective in mice receiving intratracheal bleomycin. In a subsequent paper, they attribute these findings to Tβ4-mediated reduction in the numbers of IL-17 producing cells in circulation as well as decreased IL-17 levels in the lung tissue(44). A potentially therapeutic peptide derived from endostatin was described by Yamaguchi *et al.* (45) and ameliorated dermal and pulmonary fibrosis *in vivo* as well as in an *ex vivo* human skin model.

In a recent randomized, double blinded clinical trial, SSc patients treated for six months with the commonly used fluoroquinolone, ciprofloxacin, vs. placebo experienced decreased skin fibrosis (46). The mechanism of this effect, however, remained unclear. An *in vitro* study by Bujor *et al.*(47) examined the antifibrogenic effect of ciprofloxacin on dermal and lung fibroblasts from SSc patients vs. controls. Ciprofloxacin treatment reduced type I collagen production and connective tissue growth factor (CCN2) gene expression, and increased levels of matrix metalloproteinase 1 (MMP1). The antifibrotic effects of ciprofloxacin were felt to be due to down-regulation of DNA methyltransferase (Dnmt1), up-regulation of friend leukemia integration factor 1 (Fli1), and induction of MMP1 via an ERK1/2-dependent mechanism.

Increased numbers of circulating fibrocytes— bone marrow-derived fibroblast precursors that co-express leukocyte (CD45+) and fibroblast markers (col1+)— have been reported in the blood of patients with IPF, especially in the setting of acute exacerbation(48), and also in patients with SSc(49). Borie *et al.*(50) investigated whether fibrocytes were recruited to the

alveolar space in IPF and SSc. They found that fibrocytes were detected in BAL in only about half of the IPF and SSc patients studied and were therefore not a good prognostic marker.

Another type of stromal cell, the telocyte (CD34+, CD31−), may be important in the pathophysiology of SSc. These cells possess extremely long cytoplasmic processes and are thought to form a three-dimensional scaffold that aids in cellular organization and tissue renewal and repair after injury. Previous SSc studies have demonstrated loss of telocytes from affected skin(51). Manetti *et al.*(52) stained tissue from the stomach, heart, and lungs of patients with SSc vs. controls and found that telocyte loss was not confined only to skin but rather evident in all of these organs. Loss of these particular stromal cells may therefore be a key step along the pathway to development of fibrosis.

Joseph *et al.*(53) examined scleroderma patients with cancer as a distinct subset. Drawing on the observation that SSc patients with autoantibodies to RNA polymerase III subunit (RPC1) demonstrate an increased incidence of cancer, they analyzed tumors from SSc patients with RPC1 autoantibodies vs. patients with topoisomerase 1 (TOP1) or centromere protein B (CENPB) autoantibodies. 75% of the tumors from SSc patients with RPC1 autoantibodies displayed genetic mutations in the polymerase III polypeptide A gene (POLR3A) while none of the tumors from the control patients did. Subsequent analysis of peripheral blood lymphocytes and serum suggested that POLR3A mutations triggered cellular immunity and that cross-reactive humoral immune responses may have contributed to the development of scleroderma.

Conclusion

Systemic sclerosis is a heterogeneous autoimmune disease where patients present with a wide range of skin and organ involvement as well as with different rates of disease progression. Despite its challenges, significant progress has been made over the past year in our understanding of various clinical aspects. Two new animal models that more faithfully replicate human disease have emerged and will be useful in experimental studies. Finally, many promising areas of study have been identified, some of which should lead to more effective therapies for SSc than we currently have.

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Key points

1. The pathogenesis of SSc-ILD remains incompletely understood in spite of recent advances in identifying signatures associated with lung disease.
2. Research into SSc-ILD will be facilitated by the availability of two new mouse models of lung disease.
3. New imaging strategies will facilitate monitoring of lung disease progression in scleroderma patients.