Interstitial Lung Disease in Scleroderma

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KEYWORDS

• Systemic sclerosis • Interstitial lung disease • Fibrosis • Pathogenesis • Diagnosis • Treatment

KEY POINTS

- Interstitial lung disease is a significant cause of morbidity and mortality in systemic sclerosis.
- Diagnostic modalities to assess interstitial lung disease include pulmonary function tests, which may show decreases in the forced vital capacity and diffusion capacity of the lung for carbon monoxide, and high-resolution computed tomography, which may show patterns consistent with nonspecific interstitial pneumonia or usual interstitial pneumonia.
- Pathogenesis revolves around an interplay of vascular injury, inflammation, and subsequent fibrosis, with transforming growth factor-beta playing a key role in fibrosis.
- Effective treatment modalities are limited, with cyclophosphamide being the most rigorously studied treatment. Therapies that are often used in other autoimmune conditions are not as effective in systemic sclerosis-interstitial lung disease.
- Several alternative treatment approaches are being considered, including rituximab, bosentan, tyrosine kinase inhibitors, pirfenidone, and hematopoietic stem cell transplant.

INTRODUCTION

Systemic sclerosis (SSc) is a heterogeneous disease characterized by vasculopathy, autoimmunity, and fibrosis, with multiorgan involvement and no known cure. Pulmonary complications of SSc remain one of the largest causes of morbidity and mortality in the disease. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the most common forms of lung disease associated with SSc. This review focuses on SSc-ILD, a leading cause of mortality in SSc. Pulmonary function tests (PFTs) and chest imaging with high-resolution chest tomography (HRCT) remain important tools

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in the diagnosis and prognosis of SSc-ILD. Although significant advances have been made in the understanding of the pathogenesis of SSc-ILD, current treatment options have limitations in their overall effectiveness. Several treatment modalities are currently under investigation, and novel targeted treatments that have shown promise in idiopathic pulmonary fibrosis (IPF) clinical trials may ultimately be useful in SSc. This review provides a brief overview of SSc-ILD pathogenesis to date, and includes a discussion of key points in the evaluation and management of the disease, including a discussion on novel therapies.

EPIDEMIOLOGY

ILD is common in patients with SSc, with up to 90% of patients exhibiting evidence of interstitial changes on HRCT,[1] and between 40% and 75% of patients having PFT abnormalities.[2,3] Clinically significant lung fibrosis is present in approximately 25% of all SSc patients,[4] but there is significant heterogeneity with regard to the incidence of pulmonary involvement based on several factors, including the SSc subset and antibody profile. In particular, patients with diffuse cutaneous SSc (dcSSc) or Scl-70 (antitopoisomerase) antibodies are at higher risk for ILD development, whereas patients with limited cutaneous SSc or anticentromere antibodies less commonly have ILD. Among 3656 patients in the European League Against Rheumatism (EULAR) Scleroderma Trials and Research database, 60% of patients with positive Scl-70 antibodies had evidence of ILD compared with 21% of patients with anticentromere antibodies.[5] Certain clinical features, such as African-American ethnicity, modified Rodnan Skin Score (mRSS), serum creatinine level, creatine phosphokinase values, and evidence of cardiac involvement are also found to be independent predictors of lung involvement in SSc.[4] In a recent meta-analysis looking at predictors of mortality and progression in SSc-ILD, factors including older age, lower forced vital capacity (FVC), and lower diffusing capacity of the lungs for carbon monoxide (DLCO) predicted mortality.[6] Extent of disease involvement on HRCT predicted both mortality and ILD progression.

Several biomarkers have been studied as possible predictors of the development and progression of ILD in SSc. These markers, which are currently not available for clinical use in the United States, may play a role in prognosis and disease monitoring in the future. Specifically, the glycoproteins Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) are found to be elevated in patients with SSc-ILD, and levels may correlate with ILD severity and progression.[7,8]

PATHOGENESIS

The pathogenesis of SSc-ILD is multifactorial and incompletely understood. Endothelial cell injury with subsequent vascular damage and alveolar epithelial cell injury are key initial insults that precede fibrosis. At the time of injury, various mediators are released, and fibroblasts are activated. Over time, fibroblasts acquire features of smooth muscle cells and become myofibroblasts, resulting in dysregulated accumulation of collagen and extracellular matrix components and ultimately fibrosis (**Fig. 1**). Some of the mediators implicated in SSc-ILD include thrombin, transforming growth factor-beta (TGF-β), and the Wnt/β-catenin pathway.

Thrombin

Lung biopsies of SSc-ILD patients show evidence of endothelial and epithelial injury with interstitial edema.[9,10] Endothelial cell injury results in thrombin production and release of endothelin-1 with elevated levels of thrombin detected in bronchoalveolar lavage fluid of SSc patients compared with healthy controls.[11] Inhibition of thrombin