INTRODUCTION

Systemic sclerosis (SSc) is a multisystem connective tissue disease of unknown etiology. Similar to other connective tissue diseases, SSc follows a chronic course, occurs more commonly in women, and is highly heterogeneous in its protean clinical manifestations. The hallmarks of SSc are autoimmunity and inflammation, functional and structural abnormalities in small blood vessels in multiple vascular beds, and progressive interstitial and vascular fibrosis in the skin and internal organs. Systemic Sclerosis (SSc) is classified as shown in Table I.

SSc is characterized by three major processes which include disease-specific autoantibodies; organ fibrosis that can involve several body systems, including the pulmonry, integument, cardiac, gastrointestinal, renal systems; and small-vessel vasculopathy.

LUNG INVOLVEMENT IN SYSTEMIC SCLEROSIS

The respiratory system is frequently affected in the systemic sclerosis and contributes to significant morbidity and mortality. Involvement can occur in all aspects of the respiratory tract including, the blood vessels, airways, pleura, parenchyma, and musculature. The respiratory manifestations of systemic sclerosis are variable and listed in Table II.1

INTERSTITIAL LUNG DISEASE (ILD)

Inflammation or fibrosis involving the pulmonary interstitium denotes a group of disorders referred to as ILD. ILD is the most common pulmonary manifestation in SSc, with 40% of patients having restrictive changes on pulmonary function tests (PFT) and more than 90% of patients having evidence for ILD at autopsy. Interstitial lung disease develops

Table I. Classification of Systemic Sclerosis (SSc)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited cutaneous (lc SSc)</td>
<td>Skin thickening restricted to sites distal to elbows and knees, but may involve face and neck</td>
</tr>
<tr>
<td>CREST syndrome</td>
<td>Subset of limited cutaneous SSc with prominent calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia</td>
</tr>
<tr>
<td>Diffuse cutaneous (dcSSc)</td>
<td>Skin thickening on the trunk and proximal extremities in addition to distal extremities and face</td>
</tr>
<tr>
<td>Overlap SSc</td>
<td>Skin changes and other characteristic features of SSc coexisting with features of another connective tissue disease, including systemic lupus erythematosus, myositis, or rheumatoid arthritis</td>
</tr>
<tr>
<td>SSc sine scleroderma</td>
<td>Raynaud’s phenomenon, characteristic internal organ complications, and serologic abnormalities of SSc, but no apparent skin involvement</td>
</tr>
</tbody>
</table>
Interstitial Lung Disease (ILD)

- Nonspecific interstitial pneumonia (NSIP)
- Usual interstitial pneumonia (UIP)
- Diffuse Alveolar damage (DAD)
- Cryptogenic organizing pneumonia (COP)

Pathological Types of SSC-ILD
Following pathological types of ILD are seen in SSc.

<table>
<thead>
<tr>
<th>Table II. Respiratory Manifestations of Systemic Sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial Lung Disease (ILD)</td>
</tr>
<tr>
<td>- Nonspecific interstitial pneumonia (NSIP)</td>
</tr>
<tr>
<td>- Usual interstitial pneumonia (UIP)</td>
</tr>
<tr>
<td>- Diffuse Alveolar damage (DAD)</td>
</tr>
<tr>
<td>- Cryptogenic organizing pneumonia (COP)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Pleural involvement</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td>Alveolar hemorrhage</td>
</tr>
<tr>
<td>Small airways disease</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Respiratory muscle weakness</td>
</tr>
<tr>
<td>Drug-induced toxicity</td>
</tr>
<tr>
<td>Spontaneous pneumothorax</td>
</tr>
<tr>
<td>Pneumoconiosis (silicosis)</td>
</tr>
</tbody>
</table>

Insidiously and generally progresses to fibrosis. Because lung fibrosis is irreversible, early diagnosis is vital to reduce morbidity and mortality.

Investigation and assessment of interstitial lung disease in SSC focuses on early detection, assessment of severity, and determination of progression and is best performed by regular pulmonary function tests. High-resolution computed tomography (CT) remains the most valuable tool for detection of early lung involvement.

Pathogenesis
The pathogenesis of ILD, including SSC-ILD, remains uncertain. There is a complex interplay between inflammatory activation, immunologic phenomena, and vascular injury. There is evidence based on many studies for an imbalance between profibrotic and antifibrotic factors in of bronchoalveolar lavage fluid. Myofibroblasts express a smooth muscle actin which is associated with fibrotic lesions in presence of tumor necrosis factor-alpha (TNFα), transforming growth factor-β (TGF-β), connective tissue growth factor (CTGF, CCH2), platelet-derived growth factor (PDGF), interleukin (IL)-1α, IL-8, IL-10 and macrophage inflammatory protein-1a (MIP-1a). Decreased levels of antifibrotic factors like caveolin-1 and hepatocyte growth factor promote fibrosis.

1. Non-Specific Interstitial Pneumonia (NSIP): This is the most frequent finding in patient with systemic sclerosis (68-78%) which is diffuse and spatially homogeneous. There are two forms of NSIP:
   - Cellular NSIP, which is characterized by lymphocytic and plasma cell infiltrates with minimal fibrosis; and
   - Fibrotic NSIP, which is characterized by fibrotic changes, either alone or in combination with patchy areas of inflammation.

2. Usual Interstitial Pneumonia (UIP): UIP is seen in 8-26% of patients with SSC. It is characterized by a heterogeneous pattern in which areas of normal lung are interspersed with areas of active fibrosis (known as fibroblastic foci), interstitial inflammation, and honeycombing. The changes are usually most pronounced in the subpleural lung. UIP demonstrates “temporal heterogeneity” in that new, active areas of fibrosis can be found adjacent to areas of more advanced fibrosis and honeycombing in a pattern reflective of ongoing, repetitive lung damage. It is unresponsive to treatment with corticosteroids and is seen more commonly in patients of rheumatoid arthritis.

3. Organizing Pneumonia (OP): Pathologic findings in OP consist of plugs of granulation tissue called Masson bodies extending into lumens of the bronchioles and alveoli and obstructing the airways, these plugs of tissues are composed of inflammatory cells, debris, fibrin, myofibroblasts, and immature connective tissue.

SSc associated ILD corresponds to non-specific interstitial pneumonia (NSIP) in most cases, whereas usual interstitial pneumonia (UIP) is encountered less frequently. This explains the better prognosis of SSc associated ILD compared to idiopathic pulmonary fibrosis (IPF). Those with the UIP pattern of disease had a trend toward shorter survival time.

Clinical features
Patients may be asymptomatic in early stages. Later on complaints include dyspnoea on exertion and non-productive cough, productive cough indicates hemorrhage, neoplasm, infection or aspiration. Fine inspiratory Velcro crackles at lung bases is a common finding. Clubbing is rare with SSc as sclerodactyly is superimposed. Ultimately patients may develop cor pulmonale.

Investigations
Autoantibodies
Autoantibodies found in SSc and their correlate with ILD is shown in Table III.
Pulmonary Function Test
PFT with measurement of DLCO should be undertaken routinely as a screening for early ILD. The role of PFT is above all diagnostics; they also allow determination of the clinical impact of the interstitial lung disease by accurately evaluating its severity. PFT provides prognostic information and allow assessment of the response to treatment. Pulmonary involvement is defined by a TLC and/or FVC less than 80% and/or a DLCO less than 75%. Changes in PFT occurs before symptoms, hence patient should undergo PFT every 3 to 6 months, depending on disease worsening. The functional profile shows a restrictive defect of variable severity associated with an alteration of alveolar-capillary function and hypoxemia on exercise. This is often less marked than in idiopathic pulmonary fibrosis.

The measurement of arterial oxygen saturation is best performed with a frontal electrode. Digital and aural electrodes do not allow reliable measurement of saturation in patients with severe Raynaud's syndrome.

The presence of an early reduction in FVC is the most important risk factor for progression in ILD. Measured within the first 3 years from disease onset, baseline FVC may predict deterioration of pulmonary function in patients with scleroderma. Patients with normal pulmonary function at initial assessment are at low risk to develop considerable impairment of pulmonary function.\(^5\)

6 min walk test (6MWT)
The objective of this test is to walk for 6 minutes. During the test patient is permitted to slow down, stop or lean against the wall. However walking should be resumed once the patient is better. Test is terminated if the saturation of oxygen by pulse oxymetry is less than 80% or if patient experiences chest pain or leg cramps.

Total distance walked (6MWT distance), and baseline and post-test Borg Dyspnoea Indices are documented. Borg Dyspnoea Index is a well-validated scoring system (on a 0-10 point scale) to gauge a person’s perceived effort of exertion and degree of fatigue experience (0=nothing at all, 10=maximum).

In a multicenter study of 163 patients of systemic sclerosis with ILD 6MWT was used as an outcome measure in ILD. The 6MWT distance weakly correlated with Borg Dyspnoea Index, FVC and DLCO. The lack of correlation of 6MWT with standard physiological parameters of ILD suggests a multifactorial basis for limited exercise capacity in patients with SSc and calls into question the utility of the 6MWT as a measure of outcome SSc-ILD.\(^6\)

High Resolution Computerized Tomography (HRCT)
The application of high-resolution CT has been of immense value for definition and assessment of diffuse lung diseases and has revealed the character and distribution of fine structural abnormalities not visible on chest radiographs. The earliest detectable high-resolution CT abnormality is a narrow, often ill-defined, subpleural crescent of increased density in the posterior segments of the lower lobes. When more extensive, the shadowing takes on a characteristic reticulonodular appearance and becomes associated with fine, honeycomb airspaces and ultimately large cystic airspaces, an appearance that mirrors the macroscopic picture.

1. Ground Glass Opacity (GGO), increased lung attenuation, is believed to be associated with an active inflammatory process.
2. Pulmonary Fibrosis, reticular interstitial thickening with traction bronchiectasis or bronchiolectasis, are typically bilateral, spatially uniform, and predominantly in the bases of the lungs.
3. Honeycomb cysts (HC, clustered air-filled cysts with visible walls) are more commonly associated with UIP and are typically present with reticular findings that are bilateral, spatially inhomogeneous, peripheral or subpleural, and occur predominantly in the bases of the lungs.

HRCT derived assessment of Lung Fibrosis by Warrick Scores is a semiquantitative evaluation of radiological involvement, which provides a score for each lesion based on the severity
Bronchoalveolar Lavage (BAL)
The analysis of bronchoalveolar lavage fluid (BALF) in diagnosis and management of SSc-ILD has recently been questioned; it has provided insight into pathogenesis, through analysis of cellular and noncellular components from bronchoalveolar lung units. It is useful in differential diagnosis of other entities that might overlap, such as infection or malignancy. Bronchoalveolar lavage is not needed to evaluate disease activity in SSc-ILD.

Newer Techniques
1. **CT Densitometry**: Computerized based scoring system to measure Lung attenuation is used to assess ILD.
2. **Sonography**: Ultrasound lung comet tails (ULCs), an echographic image of multiple comets fanning out of lung surface correlate with fibrosis.

TREATMENT
The mainstay of treatment modalities includes immunosuppressive agents, lung transplantation and stem cell transplantation.

Immunosuppressive Agents
The mainstay of therapy for SSc-associated interstitial lung disease has long been corticosteroids or cyclophosphamide or both, given orally or as intermittent intravenous bolus. Two randomized controlled trials completed more recently showed a modest benefit for cyclophosphamide over placebo.

Cyclophosphamide (CYC) taken for 1 year had a modest, but significant, effect on improving lung function (changes in FVC and TLC), dyspnea (transitional dyspnea index scores), health-related quality of life (health transition and vitality) and skin scores (thickening).

Oral cyclophosphamide in patients with symptomatic scleroderma-related interstitial lung disease had a significant but modest beneficial effect on lung function, dyspnea, thickening of the skin, and the health-related quality of life. However effects on lung function were maintained through the 24 months of the study. Patients with rapidly progressive ILD might benefit from pulsed intravenous cyclophosphamide combined with prednisone 15 mg daily. A 1-year course of treatment of SSc-ILD with CYC was associated with treatment-related changes in FIB scores on HRCT scans, which correlated with other measures of treatment response. Persistently abnormal results on BAL fluid analysis following CYC treatment is a common finding and does not predict a subsequent decline in lung function. High-dose prednisolone with pulse CYC can either improve or stabilize lung functions in patients with severe systemic sclerosis lung disease irrespective of presence of ground glass appearance on HRCT.

PDGF receptor (PDGFR) amplification has been postulated to cause fibrosis in ILD and hence imatinib, PDGFR inhibitor is tried in SSc-ILD. A combination of oral imatinib (200 mg/day) and intravenous CYC (500 mg every 3 weeks) showed clinical improvement in patients with mild restrictive disease. Thus early treatment with this combination therapy may be useful.

A treatment protocol of prednisone (20 mg QOD) with 6 monthly infusions of cyclophosphamide (600 mg/m²) followed by oral azathioprine (2.5 mg/kg/day) has shown good effects. This has revealed a favorable outcome for FVC of 4.19% without any improvements in DLCO.

Endothelin is implicated as a participatory pathway in SSc. Bosentan, a nonselective endothelin receptor antagonist was tried as therapy for ILD secondary to SSc; however it showed no improvement in exercise capacity.

A study has shown that in patients with dSSc and recent, clinically apparent alveolitis, early treatment with MMF and small doses of corticosteroids (CS) may represent an effective, well-tolerated and safe alternative therapy.

A current phase III trial is underway comparing Cyclophosphamide with mycophenolate mofetil (MMF) in the treatment of active SSc-ILD. Rituximab (375mg/m²) an anti-CD20 monoclonal antibody is recently been explored as a treatment option. A recent small study was performed on 14 patients with SSc-ILD to assess the possible efficacy of rituximab. It showed improvement in median FVC% predicted and DLCO% predicted in patients treated with rituximab compared with controls, respectively.

In idiopathic pulmonary fibrosis, more recent clinical trials of pirfenidone, etanercept, IFN-γ, anti-CTGF antibodies, halofuginone, tyrosine kinase inhibitors (imatinib mesylate, dasatinib, nilotinib) and acetylcysteine have shown some efficacy, and these agents are currently undergoing further evaluation. The management of lung fibrosis in SSc is likely to be informed by the results from idiopathic pulmonary fibrosis studies.
Lung Transplantation
For selected SSc patients with advanced pulmonary involvement, lung transplantation may be an option. Single lung transplant is now considered to be the most successful transplantation approach for interstitial lung disease and for PAH.

Stem Cell Transplantation
Autologus/allogenic hematopoietic stem cell transplantation is currently ongoing phase III trials in US and Europe.

PREDICTORS OF MORTALITY
Severe lung involvement can be associated with mortality which is related to age ≥65 years, forced vital capacity <50% predicted, absence of anticentromere antibodies, and chest radiograph suggestive of pulmonary fibrosis. Also, HLA alleles DRB1*0802 and DQA1*0501 are significant predictors of mortality in addition to the predictors mentioned above.19

In Genetics versus Environment in Scleroderma Outcome Study (GENISOS), number of baseline variables including antibody status, African American ethnicity, disease type, baseline PFT values, modified Rodnan Skin Score, fibrosis on chest radiograph, lung and skin subscores of severity index were associated with serially measured forced vital capacity (FVC) levels. Also, anti-topoisomerase antibody (ATA) was the only baseline variable, associated with differential FVC levels, predicting the rate of decline in FVC within the first three years of follow up.20

PULMONARY ARTERIAL HYPERTENSION (PAH)
PAH is defined as an elevation in the mean pulmonary artery pressure greater than 25 mm Hg at rest, occurs in limited and diffuse cutaneous forms of SSc and is a leading cause of mortality. The outcome in SSc-associated PAH is considerably worse than that of idiopathic PAH.

Isolated pulmonary hypertension (PHT) in scleroderma, occurring without other pulmonary pathology, is characteristic of limited cutaneous systemic sclerosis, especially in the classical CREST form of this subset with florid cutaneous telangectasias. Secondary pulmonary hypertension in association with pulmonary interstitial fibrosis is driven by hypoxia and the destruction of the pulmonary vascular bed.

Treatment
In the absence of contraindication, supportive therapy with diuretics, oral anticoagulation, and in some cases digoxin is considered. Patients with functional class III disease are eligible for advanced therapy. Begin treatment with an oral ET-1 receptor antagonist (Bosentan nonselective versus ambrisentan selective) when functional class III is reached; lack of response prompts switching to a phosphodiesterase inhibitor (sildenafil), whereas partial response or transient response generally results in addition of a phosphodiesterase inhibitor. Further deterioration can be managed by adding inhaled iloprost or parenteral prostacyclin. Although surgical intervention may be useful for symptom control (septostomy) or long-term benefit (single lung transplant), these approaches are feasible in only a small number of SSc patients.

DRUG-INDUCED PULMONARY DISEASE
Penicillamine has been associated with bronchilolitis obliterans and Goodpasteure syndrome. Cyclophosphamide induced lung toxicity is associated with an early onset pneumonitis felt to be reversible and amenable to treatment with corticosteroids, and a late-onset pneumonitis coupled with pleural thickening that is progressive and fairly unresponsive to corticosteroids.

ASPIRATION PNEUMONIA
As a result of esophageal dysmotility and an incompetent lower esophageal sphincter, aspiration of gastric content occurs frequently in SSc. Aspiration pneumonia should be suspected in any patient with SSc presenting with pneumonia or cough, especially if there is an overlap or related myositis that might increase the risk for aspiration.

PNEUMOCONIOSIS
There is a known association between inhalational silica exposure and SSc, and an entity linking SSc with exposure to silica particles, with or without the development of silicosis, is called the Erasmus syndrome.

CONCLUSION
Lung involvement is not uncommon with systemic sclerosis. It is associated with increased mortality and morbidity. HRCT sensitive and specific than Chest X Ray. Immunosuppressive Therapy should not be deferred too long and should be started with corticosteroids especially in early phase before irreparable fibrosis occurs.
REFERENCES


