CHAPTER

15 Scleroderma and Lung

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INTRODUCTION

Scleroderma is a chronic systemic disease of unknown cause, affecting around 15 persons in one million inhabitants in all parts of the world, but most frequently women between 40–60 years of age. Until recently, scleroderma was considered to be a disease with gloomy prognosis and no cure. The general attitude has changed during last decades due to successful treatment of scleroderma renal crisis with ACE inhibitor drugs with consequent dramatic decrease of mortality. Today the pulmonary complications, interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the leading cause of death.[1] Several studies showed that the disease modifying drug, cyclophosphamide, can reduce the progression of scleroderma ILD in patients with early symptomatic disease with stabilization and also improve the extent of skin indurations. Pulmonary vasodilators have been shown to improve exercise tolerance and slow the rate of clinical deterioration in PAH. Improved survival in scleroderma is associated also with better ascertainment of internal organ disease.[2] All these data combined, contribute to the changing attitude towards scleroderma patients, with certain groups already having moderately better prognosis and other emerging towards the same goal.

The lung disease has the worst prognosis and governs the destiny of patients with scleroderma.

DEFINITION

Definition of Scleroderma

Scleroderma is characterized by thickening of the skin and thus the name scleroderma was coined, as in Greek word *skleros* means hard or indurate and *derma* means the skin.

Scleroderma is a chronic systemic disease characterized by skin indurations and thickening; by various degrees of tissue fibrosis and chronic inflammatory infiltration in diverse internal organs (lung, gastrointestinal tract, heart, and kidneys); prominent fibroproliferative vasculopathy; and humoral and cellular immune alterations.

In early phase of scleroderma inflammatory processes dominate. They are followed by almost ubiquitous functional and structural alterations in vascular beds and progressive visceral organ dysfunction due to fibrosis. The clinical features of scleroderma are highly diverse. Patients with systemic scleroderma [synonym: systemic sclerosis (SSc)] can be classified into two distinct subsets, according to distribution and extent of skin changes and other clinical and laboratory indicators, into diffuse and limited cutaneous scleroderma (Table 15-1). Diffuse cutaneous scleroderma presents with progressive skin indurations, starting in the fingers, and ascending from distal to proximal extremities, the face, and the trunk. These patients are at risk for early pulmonary fibrosis and acute renal involvement. In limited scleroderma, patients generally have longstanding Raynaud's phenomenon before other manifestations of scleroderma appear. Skin indurations are limited to the fingers, distal extremities, and face; and the trunk is not affected. A subset of patients with limited disease have prominent calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactily, and telangiectasia, a constellation termed CREST syndrome. However, these features may also be seen in patients with diffuse cutaneous scleroderma. Although the long term prognosis in limited cutaneous scleroderma is better than that of diffuse PAH, hypothyroidism and primary biliary cirrhosis may occur in the late stage of the former. In some patients, Raynaud's phenomenon and other typical features of scleroderma occur in the absence of detectable skin thickening. This syndrome has been termed scleroderma sine scleroderma.

Table 15-1 Subsets of Scleroderma [Synonym: Systemic Sclerosis (SSc)]

Features	Limited cutaneous	Diffuse cutaneous
Skin involvement	Limited to fingers, distal to elbows, face; slow progression	Diffuse: fingers, extremities, face, trunk; rapid progression
Raynaud's phenomenon	Precedes skin involvement	Onset contemporaneous with skin involvement
Pulmonary fibrosis	May occur, moderate	Frequent, early, and severe
PAH	Frequent, late, may be isolated	May occur, associated with pulmonary fibrosis
Sclerodermal renal crisis	Very rare	Occurs in 15%, early
Calcinosis cutis	Frequent, prominent	May occur, mild
Characteristic autoantibodies	Anticentromere	Antitopoisomerase I (Scl-70)

Definition of Pulmonary Manifestations and Complications of Scleroderma

Pulmonary manifestations and complications of scleroderma are numerous and diverse. The most frequent are PAH and ILD. Today it is the leading cause of disease-related morbidity and mortality in scleroderma patients. In a recently published study, Steen and associates[1] have shown that the overall survival of scleroderma patients improved steadily from 54-66%. On the other hand, the proportion of patients with scleroderma who died of pulmonary fibrosis increased from 6–33%. Pulmonary fibrosis is detectable in most patients with scleroderma on autopsy examination.[3] The frequency of pulmonary hypertension is also increased during this time period.

Other pulmonary manifestations and complications of scleroderma are GERD-related respiratory manifestations, airway disease, i.e., bronchiectasis/bronchiolectasis, extrinsic restriction secondary to rigid chest wall, impaired locomotion, neuromuscular disease, pleural effusion, pneumothorax infections, malignancies, and drug induced lung disease (Table 15-2).

Three types of systemic scleroderma exists, diffuse cutaneous, limited, and scleroderma sine scleroderma, which are defined by specific scope of cutaneous involvement. All variations of pulmonary manifestations have been perceived in each of scleroderma phenotypes, and one should not exclude a particular pulmonary disorder based exclusively on clinical scleroderma subtype.

The leading symptom of any pulmonary involvement in scleroderma is dyspnea. It is very difficult to differentiate the cause of shortness of breath in these patients and attribute the symptom to particular organ involvement, as it can be noticed in ILD, PAH, and numerous other clinical manifestations.

SYMPTOMS AND SIGNS OF PULMONARY INVOLVEMENT IN SCLERODERMA

Respiratory symptoms in scleroderma lung disease can be quite nonspecific. At early stage, for instance, pulmonary fibrosis can advance without any symptoms. The fact that the pulmonary manifestations are the leading cause of morbidity and mortality prompts the efforts to detect the respiratory involvement as early as possible. The precise staging and the timely institution of therapy influence the outcomes of scleroderma.

Dyspnea is the symptom usually first noticed on exertion, but with progression it is also present at rest. The cough is often dry and nonproductive. The tightness of chest is often reported, along with some nonspecific symptoms for instance the fatigue.

Dyspnea could be due to ILD, some infrequent pulmonary manifestations, such as bronchiectasis/bronchioloectasis, diffuse alveolar hemorrhage or its cause could be extrapulmonary like cardiac involvement, especially the left ventricular diastolic

Table 15-1 The Influence of Scleroderma Upon the Respiratory Structure and Function

Interstitial lung disease • Fibrotic NSIP • Cellular NSIP • UIP • BOOP • DAH	Most frequent is fibrotic NSIP, where the cellular is quite rare as well as the UIP variation.
Pulmonary hypertension • Pulmonary vasculopathy • Secondary to ILD • Secondary to cardiomyopathy (especially with diastolic dysfunction) • Chronic thromboembolic disease	The prevalence differs from 8–32% of all patients with scleroderma.
Airway disease • Bronchiectasis • Bronchioloectasis • Follicular bronchiolitis	Symptomatic airway disease is relatively uncommon.
Pleural involvement • Adhesions and thickening • Effusion • Pneumothorax	Symptomatic pleuritis is relatively uncommon.
GERD associated • Aspiration pneumonia • Cough • Asthma-like symptoms • Wheezing • Hoarseness	Gastroesophageal reflux is considered a contributing factor in the pathogenesis of ILD in scleroderma.
Motility of the thoracic cage • Restricted joint motion • Extensive skin tightness • Neuromuscular dysfunction Infections • Malignancies • Drug induced lung disease	The reduction of 6-minute walking distance can be due to multiple factors, not only cardiovascular and respiratory tract affection, but also the impaired thoracic cage motility.

NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia; BOOP, bronchiolitis obliterans organizing pneumonia; DAH, diffuse alveolar hemorrhage; and gastroesophageal reflux disease.

dysfunction, diminished thoracic cage expansions, neuromuscular, and pleural disease. It is rather challenging for the clinician to detect the underlying causes not only of breathlessness, but also other symptoms which can be due to different or even multiple causes, like fatigue. Fatigue may be seen in scleroderma lung disease, but also in active arthritis, myositis, fibromyalgia, or cardiac disease. The development fatigue due to ILD is rather difficult to detect, as the symptoms are quite similar and they coincide partially.

Physical examination of the scleroderma patients is of utmost importance. It is to note that there is a minor group of patients with ILD, in which the ILD is the first, initial sign of scleroderma.[4] The examination is usually rewarding as in most cases there are some signs that point to scleroderma if the search is thorough.[5]

The involvement of the lungs in scleroderma may be detected by auscultation, as in some patients the bibasilar late inspiratory fine crackles are identified. Physical examination findings may include the following: P2 may be loud, and a systolic ejection murmur may be heard over left sternal border. The P2 may demonstrate fixed or paradoxical splitting. If cor pulmonale develops, the signs are high-pitched systolic murmur of tricuspid regurgitation, hepatomegaly, a pulsatile liver, ascites, and peripheral edema.

ILD IN SCLERODERMA

Clinically significant ILD in patients with scleroderma is observed in about 40% of cases, and it makes the ILD the most frequent among pulmonary manifestations. Diffuse cutaneous scleroderma is more often associated with pulmonary fibrosis, but pulmonary fibrosis also occurs in limited cutaneous forms,[6] even in scleroderma sine scleroderma.

Algorithm of diagnostic procedures in these patients does not differ considerably from the procedure of any other diffuse lung disease.

Pulmonary Function Tests

Pulmonary function tests are essential in assessment of dyspnea, and they play a crucial role in evaluation of pulmonary involvement in scleroderma. Up to 40% of scleroderma patients show at least a moderate restrictive pattern in spirometry, and 15% have severe restriction without obstruction.[7] Diffusion capacity for carbon monoxide (DLCO)[8] is more sensitive in detecting lung involvement than forced vital capacity (FVC), but less specific for ILD as pulmonary vascular disease and COPD with emphysema may also cause decreased DLCO. Impaired DLCO correlates with severity of ILD, measured as the extent of the disease on computed tomography.[9] Baseline values of DLCO and FVC have been used to measure disease severity. The decrease in both variables has been associated with increased mortality of patients

with ILD in scleroderma. In patients, symptoms of marked loss of FVC usually were noted early, during the first two years of follow-up. Careful monitoring of pulmonary function tests, early in the disease, should be carried out; when the greatest loss of lung function occurs, it may help in identifying patients who are likely to respond to new therapy. It is to note that disease severity in patients with pulmonary fibrosis due to scleroderma should be classified as mild, moderate, and severe when the measures of DLCO and FVC are 70-79%, 50-60%, and less than 50% of the predicted values.[10]

Combination of normally preserved lung volumes and considerably decreased DLCO is characteristic of presence of PAH.[11]

Imaging Studies

The characteristic chest X-ray in scleroderma patients with ILD shows linear and reticular pattern, superimposed upon the ground-glass attenuation. Traction bronchiectasis may be detected, but contrary to the finding in idiopathic pulmonary fibrosis (IPF), the honeycombing is rare (Figure 15-1). Evidence of pulmonary disease has been described in chest X-rays in 20–65% of patients affected by scleroderma.[12]

The high-resolution computed tomography (HRCT) has improved the diagnosis of multiple ILD due to its high sensitivity. In all scleroderma patients, parenchymal alterations are detected by HRCT in 55–56% of cases, and if they have abnormal pulmonary function tests, the percentage rises up to 91%.[13]

In scleroderma, the high sensitivity of HRCT method has helped to detect the pulmonary changes early in the course of the disease. The characteristic findings are ground-glass attenuation, reticular, and linear pattern, dominantly on lung bases, which resemble the HRCT finding in idiopathic nonspecific interstitial pneumonia

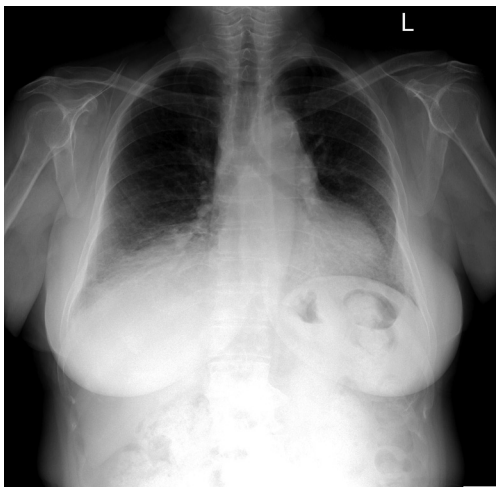


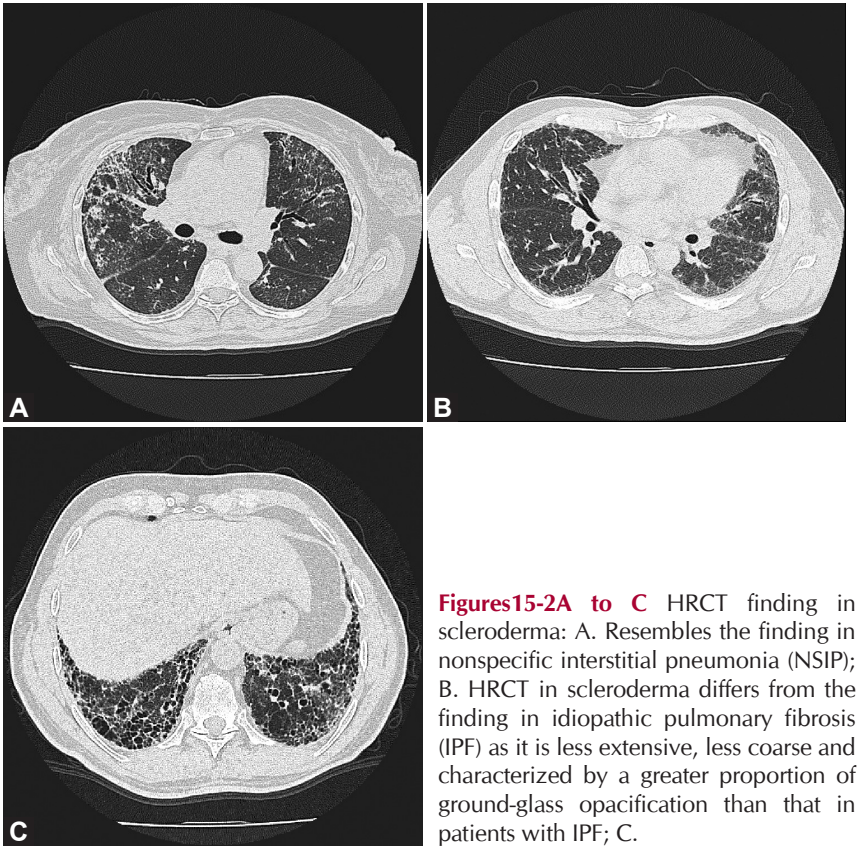
Figure 15-1 Characteristic chest X-ray in scleroderma patient with interstitial lung disease shows linear and reticular pattern, superimposed upon the ground-glass attenuation.

(NSIP).[14] HRCT finding also differs from the finding in IPF, as it is less extensive, less coarse, and characterized by a greater proportion of ground-glass opacification than that in patients with IPF (Figures 15-2A to 15-2C).

Ground-glass attenuation has been frequently attributed to alveolitis, but it seems that in most cases it presents early phase fibrosis; and only in some cases, it represents the reversible inflammatory disease. It is in accordance with biopsy finding with only less than 25% of scleroderma patients having inflammation, despite ground-glass pattern on HRCT scanning.[15]

The honeycombing pattern is not a feature of ILD in scleroderma, although in recent study, it was detected in more than 30% of symptomatic patients,[16] with a significantly higher incidence in patients with limited scleroderma compared to patients with diffuse scleroderma (Figure 15-3).

HRCT helps to detect parenchymal alterations in the early course of the disease, and can be advantageous in determining the prognosis of scleroderma patients. It has recently been shown that those patients with more extensive disease on HRCT,



Figures15-2A to C HRCT finding in scleroderma: A. Resembles the finding in nonspecific interstitial pneumonia (NSIP); B. HRCT in scleroderma differs from the finding in idiopathic pulmonary fibrosis (IPF) as it is less extensive, less coarse and characterized by a greater proportion of ground-glass opacification than that in patients with IPF; C.

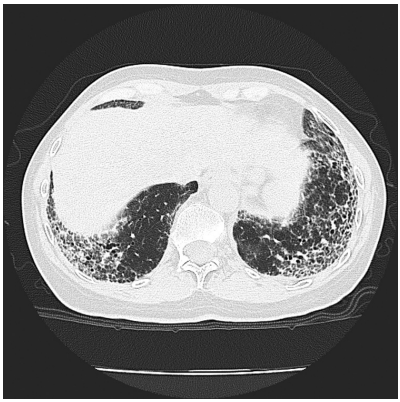


Figure 15-3 Honeycombing pattern is not a feature of ILD in scleroderma. Sometimes, it can be seen like in this patient with limited scleroderma.

i.e., abnormalities occupying more than 20% of the lung volume, had substantially higher mortality and accelerated lung function deterioration. Patients with less than 20% of the lung abnormality had no increase in long-term mortality, compared to patients with no disease on HRCT. As the prognostic information based only upon pulmonary function tests or HRCT scan is not entirely satisfactory, a simple staging system, combination of FVC measurements, and extent of ILD on HRCT provide discriminatory prognostic information[17]

Ultrasound lung comets (ULCs), a recently described echographic sign of interstitial lung fibrosis, are often found in scleroderma and more frequent in the diffuse than in the limited form of scleroderma and are reasonably well correlated with HRCT-derived assessment of lung fibrosis. They represent a simple, bedside, radiation-free hallmark of pulmonary fibrosis of potential diagnostic and prognostic values.[18]

Bronchoalveolar Lavage (BAL) and Lung Biopsy

The pathogenesis of ILD in patients with scleroderma mainly comprises the immunological inflammatory activation and vascular injury. The chronic inflammation, hypothetically in response to unrecognized injury, is believed to play a significant role in the fibrotic process. During the last three decades, the method of BAL has considerably contributed in obtaining important information, regarding the pathogenesis of ILD in patients with scleroderma.

In early days of the investigation of clinical utility of BALF analysis, i.e., of alveolitis, it was believed that the characteristic cell profiles were helpful in the management of

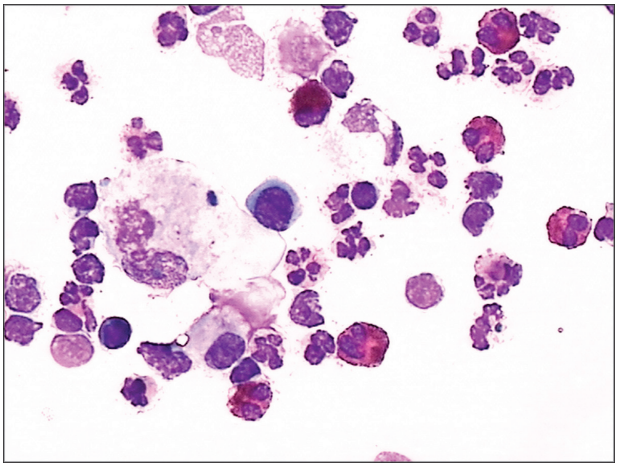


Figure 15-4 Neutrophil and eosinophil alveolitis is detected in more than 50% of scleroderma patients.

scleroderma patients with ILD. The neutrophil with or without eosinophil alveolitis is detected in more than 50% of these patients[19] (Figure 15-4).

It has been shown that high neutrophil count in lung lavage fluid is associated with early mortality,[20] that active alveolitis correlates with more severe lung function, and it also correlates with more extensive fibrosis on HRCT, but the detection of alveolitis has not been shown to independently predict the disease progression or response to cyclophosphamide at one year observation period.[21] The value of BALF analysis in predicting the course of scleroderma-ILD is of limited value, but may be useful in detecting unsuspected infection that can interfere and divert the management of these patients.

However, inconsistencies regarding technical aspects of BAL are obstacles in the reproducibility and interpretation of BAL results in various studies, and further studies are required to establish the role of BAL fluid in the clinical evaluation of scleroderma-ILD.[22]

Surgical lung biopsy represents a gold standard in the evaluation of ILD as it can show the histopathological type and degree of inflammation and degree of fibrosis. It can also show the presence of other causes of parenchymal involvement, alongside inflammation and fibrosis, like aspiration from gastroesophageal reflux or bronchoalveolar carcinoma.

Lung biopsy specimen analysis has demonstrated that the majority of scleroderma-ILD patients show the histopathological pattern of NSIP, less often usual interstitial pneumonia (UIP) or other types of ILD.[23] Most frequent is fibrotic NSIP, where the cellular as well as the UIP variation is quite rare. NSIP is a dominant pathologic pattern in 78% of cases.[15] Bronchiolitis obliterans organizing pneumonia (BOOP) is quite rare pathologic finding,[24] as well as diffuse alveolar hemorrhage (DAH).[25]

The sequel of the disease does not appear to be related to the pattern of histopathological finding, so it does not have the prognostic value. Open lung biopsy, when performed by the aid of thoracoscope, is an invasive procedure, associated with increased morbidity. The biopsy specimen analysis is seldom unequivocal, and specimen from different localizations gives different histopathologic patterns. These are the reasons that open lung biopsy is not routinely performed, especially if the HRCT finding is typical.

Therapy of Scleroderma ILD

When ILD is detected and categorized as the pulmonary manifestation of scleroderma, the therapy is considered. Initially, the physician has to decide whether it is necessary to treat scleroderma, ILD or to closely observe the patient. The initiation of therapy depends on several factors. It seems that the efficacy of treatment mainly rests upon the early verification of alveolitis. The rate of severity, according to several proposals mentioned earlier in the text (extent of HRCT fibrosis, pulmonary function tests, or combination of both) and accelerated deterioration influence the prognosis and facilitate decision to treat.

The purpose of treatment is to improve patients' quality of life, prolong survival, and decrease mortality rate. The efficacy of the medication can be estimated by several other parameters, but they are important as primary outcome measures in clinical trial, less so for the patient.

For many years, D-penicillamine has been the mainstem of antifibrotic treatment, but its efficacy in the treatment of scleroderma-ILD has not been proven.[26]

Based upon the results from two high-quality clinical trials and despite its toxicity, cyclophosphamide should be considered for the therapy of scleroderma-ILD. The efficacy and safety of cyclophosphamide were evaluated in a multicenter, prospective, randomized, double-blind, and placebocontrolled high-quality study, the Scleroderma Lung Study.[27] This clinical trial was graded Jadad score 5, and it has an A strength of recommendation. The study involved 155 patients with active alveolitis, showed effects of 1–2 mg oral cyclophosphamide daily, on lung function and health-related quality of life. Modest but significant beneficial effects were observed on lung function, dyspnea, skin thickening, and health-related quality of life. The patients were followed up after the cessation of therapy. The beneficial effects of therapy waned 12 months after discontinuation of medication, except for dyspnea which continued to be reduced. The waning of the effects of therapy is the most warring for the clinicians. It seems that early, continuous, and prolonged therapy is necessary to prevent the progression of the disease, and development of a therapeutic agent with greater and more durable efficacy and less toxicity is desirable. The side effects of cyclophosphamide, especially if it is administered on daily basis for longer period, are numerous and preceded by

hemorrhagic cystitis, malignant diseases, bone marrow suppression, and even drug induced lung disease (BOOP, lung fibrosis, diffuse alveolar damage, edema, and bronchospasm).[28,29] The strategy for application of, as today only efficient medication, the cyclophosphamide should tend to minimize the exposure. Recent study showed that the monthly intravenous pulse of cyclophosphamide in combination with methylprednisolone was well tolerated and conceived improvement and stabilization. Again, the most beneficiary was the patient in whom the therapy was initiated early in the course of the disease or in whom the disease was not severe.[30]

It is quite clear that cyclophosphamide should be used for induction therapy of most scleroderma-ILD. In early disease, combination of mycophenolate mofetil and small doses of corticosteroids, as alternative first line treatment, has shown improvement of clinically evident scleroderma-ILD.[31] In the most recent prospective open-label study of mycophenolate mofetil for the treatment of diffuse scleroderma,[32] significant improvements in skin scores, peripheral vascular involvement, and patient-perceived health status were observed. Pulmonary function studies did not worsen as expected, but instead showed a trend towards improvement. The conclusion was that controlled trials are needed to further investigate this trend for improved pulmonary function studies.

Azathioprine and mycophenolate mofetil are both used for maintenance therapy of scleroderma-ILD patients.[33] The efficacy of cyclophosphamide, as the induction therapy, followed by azathioprine was only marginal, according to recent study.[34]

Lung involvement is the leading cause of death in scleroderma, however, lung transplantation for systemic disease remains controversial. The data published from a single center in Los Angeles 2010 have not resolved multiple controversies.[35] Rates of acute rejections were significantly increased for the scleroderma compared to the IPF group. Other end-points including chronic rejection, infection, survival at one year, and pulmonary function showed no differences. The conclusion was that longer follow-up is necessary to determine the effects of gastrointestinal dysfunction and acute rejection on late allograft function in these patients.

PULMONARY HYPERTENSION IN SCLERODERMA

Pulmonary hypertension is present when mean pulmonary artery pressure is more than or equal to 25 mmHg at rest, with pulmonary capillary wedge pressure less than or equal to 15 mmHg upon right heart catheterization. It is the leading cause of mortality in scleroderma patients.[36] In recent years, some progress has been achieved in patients with PH due to scleroderma, the one-year survival rate has improved from 68 to 81% and two-year from 47 to 71%.[37] Scleroderma patients with PH have substantially poorer prognosis than individuals with idiopathic pulmonary hypertension (IPAH) and PH in other connective tissue

disease. The rate of HP in scleroderma patients varies between 8–32% in different studies, depending upon the clinical phenotype of scleroderma and detection methods used. Estimates based on echocardiographic screening (confirmed by right heart catheter) suggest that 8 (French centers) to15% (UK) of scleroderma patients develop PAH.[38] In the recent study,[39] PH was found in 32% patients on 2D-echocardiography.

A number of predisposing factors may help to identify scleroderma patients at particularly high risk of developing PH. The risk factors in different studies were older age at the onset of the disease, limited cutaneous disease, digital tip ulcers, progressive deterioration of diffusion capacity, and elevated pulmonary pressure at initial evaluation.[40]

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a marker of neurohormonal activation that is useful in the diagnosis and prognosis of various forms of PAH. The recent study[41] sought to characterize and compare NT-proBNP in a cohort of PH related to scleroderma and IPAH patients. Hemodynamics were similar, except for lower mean pulmonary arterial pressure (PAPs) in PH in scleroderma patients. NT-proBNP levels were significantly higher in scleroderma patients with PH and were more closely related to hemodynamics in PH in scleroderma than IPAH patients. NT-proBNP predicted survival in the overall cohort; however, when stratified by group, predicted survival only in PH in scleroderma group. Thus, it was shown that NT-proBNP levels are significantly higher in PH in scleroderma than IPAH patients despite less severe hemodynamic perturbations and stronger predictors of survival in PH in scleroderma patients, suggesting that neurohormonal regulation may differ between scleroderma patients with PH and IPAH.

The combination of an increased NT-proBNP level together with a decreased DLCO of less than 70% predicted the occurrence of PH during follow-up.[42]

As yet, no firm agreement has been reached on the risk factors for developing the PH in scleroderma patients.

The pathogenesis of PH in scleroderma is diverse. It includes pulmonary arteriopathy as seen in IPAH, left ventricular diastolic dysfunction resulting in pulmonary venous hypertension, loss of vascular bed as a sequel of ILD and chronic thromboembolic disease associated with hypercoagulability and the presence of antiphospholipid antibodies.

The suspicion of development of PH is followed by thorough investigation that includes pulmonary function tests, transthoracic echocardiography (TTE), chest X-ray and HRCT imaging, and finally, the right heart catheterization.

Pulmonary Function Tests

Dyspnea is usually the first symptom of PH. The symptomatic patients with scleroderma who have PH, usually have a FVC with or without DLCO less than 50%

predicted. A retrospective analysis of a group of scleroderma patients identified reduced DLCO around 4.5 years prior to the diagnosis of PH.

The solitary reduction or disproportionate, large or rapid fall of DLCO suggests PH.[43] Several groups reported the reduced DLCO for all patients with scleroderma and PH; although, the normal pulmonary function tests do not rule out the presence of PH.

The six-minute walk test (6-MWT) is a useful non-invasive method for assessing the severity of dyspnea in PH related to connective lung disease.[44] The 6-MWT is an important prognostic tool in various cardiovascular diseases. However, conflicting results have been reported in scleroderma. It has been observed that scleroderma patients without pulmonary impairment have reduced exercise capacity.[45] The explanation for these results is the abnormal vascular response to exercise, as the vascular system is one of the major target organs in this pathological condition. The false positive results of 6-MWT could also be due to anemia, musculoskeletal involvement (myopathy, arthritis, arthralgias), neurological disease, and fatigue. The reduction of 6-minute walking distance can be due to multiple factors and these results raise doubts about the specificity of the 6-MWT in this systemic disease and its relevance to monitoring therapy.[46]

Transthoracic Echocardiography

The high incidence and prevalence of PH in scleroderma, together with the ruinous course, if untreated and the possibility of sufficiently efficacious treatment, form the basis for recommendations to screen regularly for PH in patients with scleroderma.

Despite its limitations, there is presently no alternative to TTE in daily clinical practice to detect PH. It offers an effective and noninvasive means of assessing the presence of PH and also its severity. It is a helpful technique to exclude myocardial or valvular disease as potential cause of dyspnea. It also detects hypertrophy with or without enlargement of right ventricle, leftward shift, or paradoxical motion of the interventricular septum, tricuspid valve insufficiency, and pericardial effusion.

The clinicians are aware that the screening for HP is necessary, but the timing of TTE, the choice of echocardiographic parameters, and characteristics of patients with increased risk are not uniformly agreed upon.

Echocardiographic screening for PH has been suggested[47] to be performed yearly in asymptomatic patients with the scleroderma and only in presence of symptoms in other connective tissue diseases. In any case, the early detection of any PAH-related symptom should prompt a complete and careful echocardiographic assessment at any time and in any subgroup of patient with scleroderma.

In most centres, the 2D-echocardiography is used to detect suspected PH in symptomatic patient; and in a patient with an established diagnosis, it is used to asses

size of cardiac chambers, monitor biventricular function, valvular function, inferior vena cava dimensions, and pericardial effusion. PAP can be derived noninvasively using a simplified version of Bernoulli's equation to convert the driving pressure gradient measured across the tricuspid valve by 2D Doppler into systolic PAP (Figure 15-5). The peak velocity of tricuspid regurgitation method,[48] elevated right ventricle Tei-index,[49] or combination of both methods is quite reliable in detection of PH. Either of the methods can minimize the number of negative catheterizations.

The shortcomings of TTE are that it can not distinguish between elevated PAP resulting from PH or from post-capillary causes such as diastolic dysfunction of the left heart. Sometimes, it is not possible to obtain precise PAP values due to technical or patient-related causes. Caution must be taken in relying on the results of TTE findings because it has been shown both that either overestimate or underestimate the degree of PH.[50]

Chest Radiography and Computed Tomographic Scanning

Chest radiography and computed tomographic (CT) scanning may be suggestive of PH. In PH plain chest radiographs may reveal enlarged central pulmonary arteries and enlarged right ventricle.

CT is the method which portrays various parts of pulmonary vasculature including right ventricle, main pulmonary artery, peripheral, and parenchymal branches of pulmonary artery.

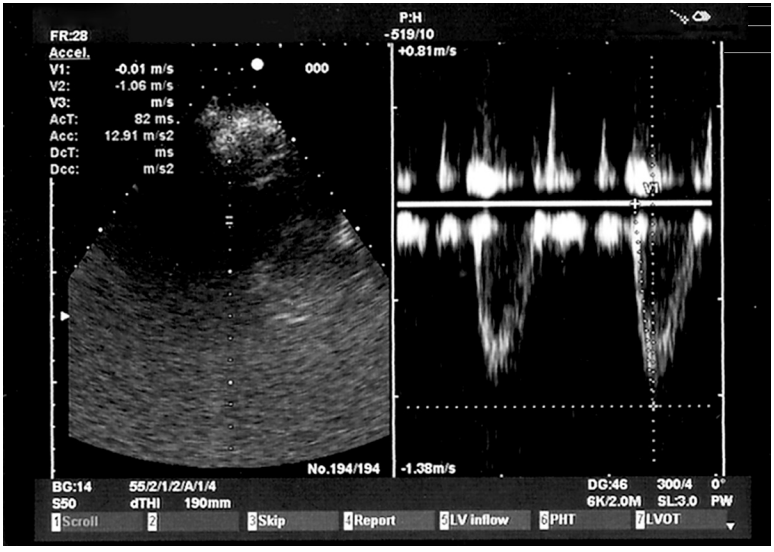


Figure 15-5 Doppler estimation of systolic pulmonary artery pressure using two-dimensional echocardiography; acceleration time of 82 ms equates to a systolic PAP of around 45 mmHg.

Cardiac signs of pulmonary hypertension on CT scans are not specific enough, except when the cardiac gated CT scans are performed. In these circumstances, the information about the size of cardiac chambers, an estimation of right ventricular ejection fraction, and congenital cardiac defects could be obtained.[51]

The size of main pulmonary artery is easily measured on CT scan (Figure 15-6). The reliability of this measure to detect PH has been investigated in several studies.[52] In Edward's study, the upper limit of normal for main PA diameter was 33.2 mm, based on 100 patients with presumed normal PA pressure.[53] Although this cut off value seems to correctly separate two populations, it is to note that the pulmonary artery size also depends on other factors, like patients size. To overcome this problem, some radiologists use the ratio of pulmonary artery size to ascending aorta size; although, it is not more specific than simple PA measurement.[54]

Segmental artery dilatation can be detected by comparing the size of the artery to adjacent bronchus; the size above 1 or 1.25 is highly suspicious to be due to high pulmonary artery pressure,[55] if detected in most lobes (Figure 15-7).

Pulmonary parenchymal signs of PH are mosaic attenuation (mosaicism), centrilobular ground-glass nodules, neovascularity, and subpleural peripheral opacities.

It seems that combination of different CT signs of PH increases the likelihood of PH in a particular patient. Finely it has been shown that the combination of CT and echocardiographic indices of PH is more closely related to mean pulmonary arterial pressure than either test in isolation.[56]

Right Heart Catheterization

Right heart catheterization remains the gold standard for diagnosis of PH. Apart the fact that PH is precisely estimated, the acute vasodilatation testing is also performed with inhaled nitric oxide, IV epoprostenol, or IV adenosine in order to determine the

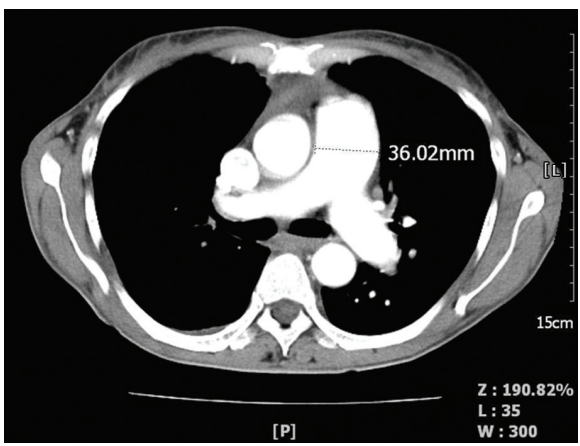


Figure 15-6 Size of main pulmonary artery is easily measured on CT scan. The size above 33.2 mm is highly suggestive of PH.

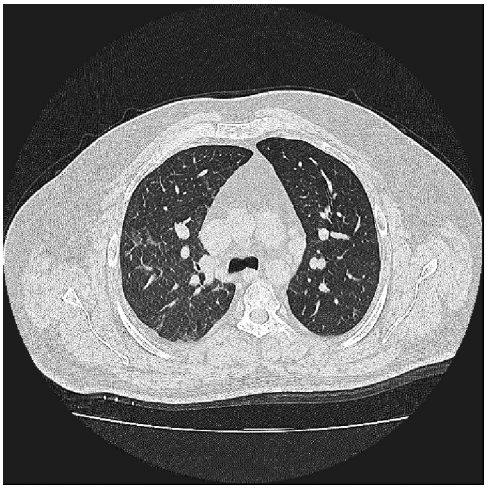


Figure 15-7 Segmental artery dilatation can be detected by comparing the size of the artery to adjacent bronchus; the size above 1 or 1.25 is highly suspicious to be due to high pulmonary artery pressure, detected in most lobes.

reversibility upon application of vasodilatators, thus choosing the most appropriate treatment for a given patient. In patients with scleroderma, it is very important to rule out the existence of the left-sided heart disease, which is a frequent cause of PH in these patients. The right heart catheterization is the only method by which it can be ruled out.

Pulmonary function tests can be helpful in detecting PH. Blood pressure in the lung can be estimated, and the size and function of the right ventricle are assessed by TTE. However, transthoracic echocardiograms are considerably inaccurate, when the PH is mild or when there is simultaneous presence of lung fibrosis.[57]

Therapy

During the last decade remarkable progress has been made in understanding the mechanisms of development of PH in scleroderma and other connective tissue disease. The processes of vasoconstriction, inflammation, vascular hypertrophy, fibrosis, and vascular remodeling have been thoroughly studied. This caused unprecedented development of new drugs that have improved the quality of life and survival of patients with scleroderma-PH.[37] The response to therapy in patients with scleroderma-PH compared to the results of IPAH is suboptimal and survival has improved, but still it is very poor. It seems that the reasons for such differences include more pronounced autoimmune, cellular and inflammatory response, and higher prevalence of comorbidities in scleroderma patients with PH, like cardiac, pulmonary venous, and interstitial lung involvement.

Therapeutic agents that have displayed benefit are the prostanoids: epoprostenol, treprostinil, and iloprost; the endothelin receptor antagonists: bosentan, ambrisentan, and sitaxentan; and the phosphodiesterase type 5 inhibitor: sildenafil.

Continuous intravenous infusion of epoprostenol has been shown to induce symptomatic and hemodynamic benefits and increase survival in scleroderma patients with PH, WHO functional class II–IV.[58] Inhaled iloprost demonstrated beneficial short-term effects in PH. Endothelin receptor antagonists (ERAs) are the first class of oral agents used to treat PH. It is to note that bosentan is also indicated to reduce the number of new digital ulcers in scleroderma and digital ulcer disease. The dual ERAs bosentan[59,60] and single ERAs sitaxentan[61] have proved effective on treating scleroderma-PH. The phosphodiesterase type 5 inhibitor sildenafil improves exercise capacity, WHO functional class, and hemodynamics in patients with symptomatic PE.[62]

The combination therapy, i.e., treating patient with more than one drug class, has become an important treatment option in these patients. The benefits of combining bosentan with epoprostenol and inhaled iloprost with bosentan have been assessed. The addition of the second drug class significantly improved the WHO functional class, hemodynamics and delayed the time to clinical worsening.

OTHER PULMONARY MANIFESTATIONS AND COMPLICATIONS

Airway diseases are uncommon findings but traction bronchiectasis may be detected, also bronchioloectasis in some cases. In the series of 49 surgical biopsies from 34 patients with scleroderma-ILD, follicular bronchiolitis was identified in 23%.[63]

Symptomatic pleuritis is relatively uncommon. Adhesions, thickening, and fibrous pleurisy are found in 90% of patients at postmortem examination. Large pleural effusions and pneumothorax are unusual.

Although any part of the gastrointestinal tract can be involved, esophageal disease occurs in nearly all patients with scleroderma. In a retrospective review of CT scans in patients with scleroderma and ILD, asymptomatic esophageal dilatation was seen in 80% of cases[64] (Figure 15-8) Most frequent esophageal manifestations are motility abnormalities and gastroesophageal reflux (GER), Barrett's esophagus, adenocarcinoma, infectious esophagitis, and drug-induced esophagitis. Extraesophageal manifestations of GER include mouth ulcers, chronic cough, hoarse voice, sore throat, pharyngitis, laryngospasm, asthma, and recurrent pneumonia.[65] Patients with scleroderma with ILD have more severe reflux (i.e., more reflux episodes and more reflux reaching the proximal esophagus). Whether or not the development of ILD in patients with scleroderma can be prevented by reflux-reducing treatments needs to be investigated.[66]

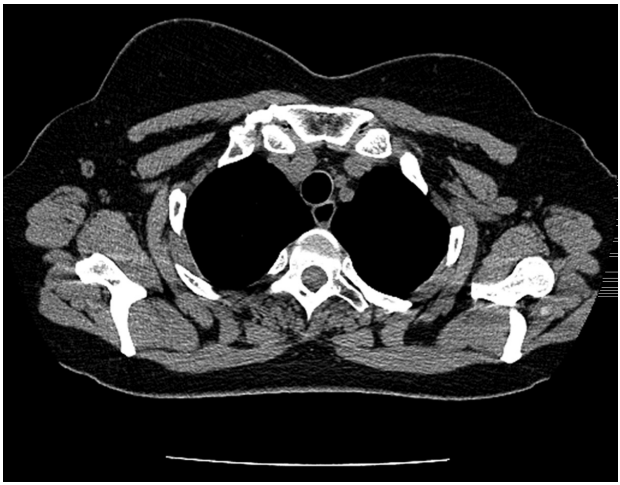


Figure 15-8 Esophageal dilatation is seen in 80% of scleroderma patients.

Motility of the thoracic cage can be compromised due to restricted joint motion, extensive skin tightness, and neuromuscular dysfunction. Muscle weakness results from deconditioning due to restricted motility and contractures, but it could also be due to myositis, especially in overlap syndromes.

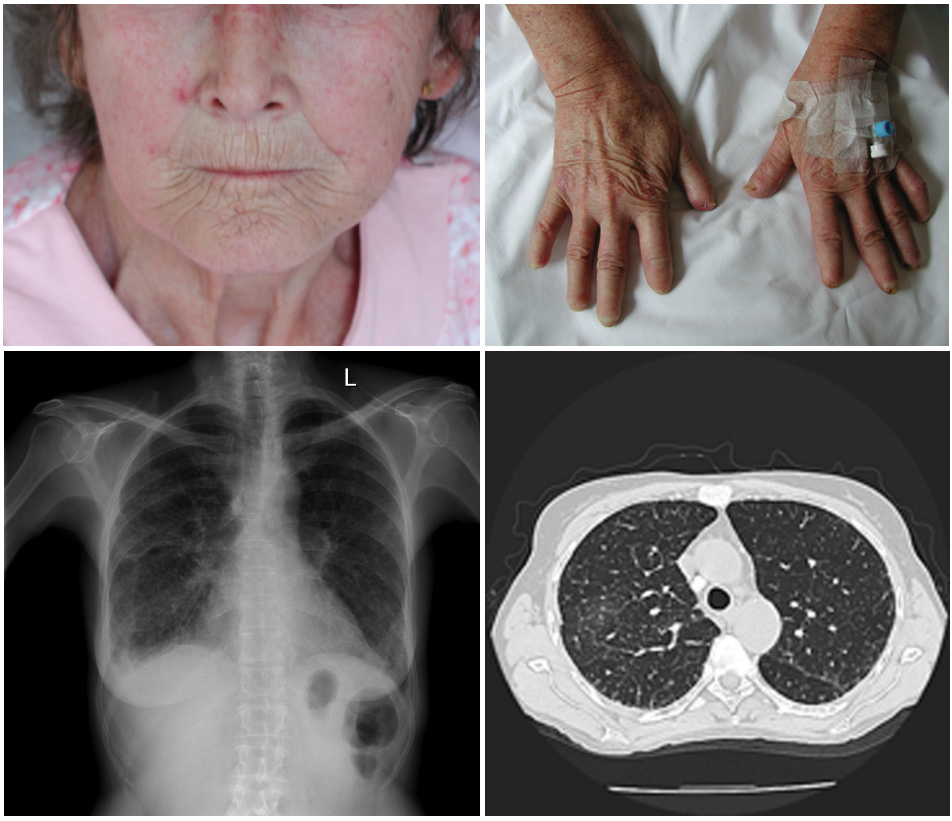
Pulmonary infections are frequent and related to the degree of structural damage and recurrent aspirations particularly in patients with severe disturbance of esophageal motility. Immunosuppressant also predispose to infection.

Malignancy is associated with scleroderma in between 3.6–10.7% of cases. Lung cancer is the most frequent type of cancer seen in patients with systemic sclerosis, followed by breast cancer. Risk factors for the development of malignancy are female gender, increased age (Figures 15-9A to 15-9 D) and diffuse systemic sclerosis.[67]

Penicillamine cyclophosphamide more frequently and azathioprine mycophenolate mofetil less frequently cause pulmonary side-effects. These data have to be considered in scleroderma patients receiving any of the mentioned drugs.

NOVEL THERAPEUTIC STRATEGIES IN LIGHT OF RECENT FINDINGS

Recent findings concerning the understanding of pathogenesis of scleroderma led to the development of entirely new lines of potentially efficacious drugs.[68] Targeted immunosuppression with T-cell directed therapies is promising. The recent inclusion of new T-cell lineage members, Th17 and regulatory T-cells (Tregs), has indicated that these subsets of effector T-cells are key regulators of inflammation in autoimmune disease.[69] Clinically beneficiary in this respect might be halofuginone which represses Th17 differentiation but not other T-cell lineages.[70] Some other



Figures 15.11A to D Risk factors for the development of pulmonary malignancy are female gender, increased age, and diffuse scleroderma. **A,** This patient suffered from scleroderma for 20 years, with gross skin lesions of the face and. **B,** hands. **C,** Chest X-ray finding aroused suspicion of the scleroderma lung affection. **D,** But the HRCT finding of interlobular septal thickening and ground-glass attenuation was atypical, suggestive only of carcinomatous lymphangitis or bronchioalveolar carcinoma. Transbronchial lung biopsy was indicated. The diagnosis was bronchioalveolar carcinoma.

promising substances with similar action are basiliximab, alemtuzumab, and abatacept.

B-cells might also be important in the pathogenesis of scleroderma, as recently published results indicate that rituximab may improve lung function and skin thickening, assessed with the modified Rodnan skin score, compared with the baseline score in patients with scleroderma.[71]

Autologous hematopoietic stem-cell transplantation is employed as a new therapeutic strategy in patients with a poor prognosis. The recently published study[72] confirms that autologous HSCT in selected patients with severe diffuse cutaneous scleroderma results in sustained improvement of skin thickening and stabilisation of organ function up to seven years after transplantation.

Imatinib mesylate is one of the first selective protein kinase inhibitors, administered orally. It is capable of selective, dual inhibition of the transforming growth factor-beta and platelet-derived growth factor pathways. The results in different preclinical models[73] of scleroderma indicate imatinib, and also dasatinib and nilotinib inhibit collagen synthesis in cultured fibroblasts and have potent antifibrotic effects in animal models of different fibrotic diseases. Moreover, several case reports, case series, and uncontrolled studies on patients with scleroderma report regression of fibrosis and good tolerability. Results of larger controlled trials are needed before any conclusions on efficacy and tolerability can be drawn. Until the results of these trials are available, off-label use of imatinib in single patient is discouraged.[74]

It has recently been shown that PPAR-gamma expression was reduced in scleroderma fibroblasts. The PPAR-gamma agonist rosiglitazone alleviated the persistent fibrotic phenotype of fibroblasts in scleroderma.[75] Thus, rosiglitazone is promising agent to combat fibrosis in diffuse scleroderma.

Targeting against endothelium-derived mediators in vasculopathy in scleroderma has already been described. Some new groups of drugs have been proposed, for instance the statins. It has been shown that they, through their vasculoprotective effects, may be beneficial in the treatment of digital vasculopathy.[76]

Studies also suggest a change in approach from monotherapy to combined therapy, as the blockade of various pathways could produce better and long-lasting results.

All these novel findings need to be confirmed by larger, multicentre, and randomized controlled clinical trials. But, already, the novel therapeutic strategies in light of recent pathogenetic findings aroused hope that the therapeutic armamentarium to combat scleroderma will be broadened in the near future.

REFERENCES

1. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis*. 2007;66:940-4.
2. Nihtyanova SI, Tang EC, Coghlan JG, et al. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study. *Q J Med*. 2010;103:109-15.
3. D'Angelo WA, Fries JF, Masi AT, et al. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. *Am J Med*. 1969;46:428-40.
4. van der Kamp R, Tak PP, et al. Interstitial lung disease as the first manifestation of systemic sclerosis. *Neth J Med*. 2007;65:390-4.
5. Peros-Golubicic T, Tekavec-Trkanjec J, Alilovic M, et al. Interstitial lung disease as the commencing manifestation of connective tissue disorders-clinical characteristics. 9th WASOG Meeting & 11th BAL International Conference. *Athens*. 2008;121-2.

6. Ostojic P, Damjanov N. Different clinical features in patients with limited and diffuse cutaneous systemic sclerosis. *Clin Rheumatol*. 2006;25:453-7.
7. Steen VD, Conte C, Owens GR, et al. Severe restrictive disease in systemic sclerosis. *Arthritis Rheum*. 1994;37:1283-9.
8. Steen VD, Graham G, Conte C, et al. Isolated diffusing capacity reduction in systemic sclerosis. *Arthritis Rheum*. 1992;35:765-70.
9. Wells AU, Hansell DM, Rubens MB, et al. Fibrosing alveolitis in systemic sclerosis: Indices of lung function in relation to extent of disease on computed tomography. *Arthritis Rheum*. 1997;40:1229-36.
10. Medsger TA Jr, Bombardieri S, Czirjak L, et al. Assessment of disease severity and prognosis. *Clin Exp Rheumatol*. 2003;21:S42-6.
11. Hsu VM, Moreyra AE, Wilson AC, et al. Assessment of pulmonary arterial hypertension in patients with systemic sclerosis: comparison of noninvasive tests with results of right-heart catheterization. *J Rheumatol*. 2008;35:458-65.
12. Arroliga AC, Podell DN, Matthay RA. Pulmonary manifestations of scleroderma. *J Thorac Imaging*. 1992;7:30-45.
13. Schurawitzki H, Stiglhaver R, Granninger W, et al. Interstitial Lung Disease in progressive systemic sclerosis: high resolution CT versus radiography. *Radiology*. 1990;176:755-9.
14. Desai SR, Veeraraghavan S, Hansell DM, et al. CT features of lung diseases in patients with systemic sclerosis: comparison with idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia. *Radiology*. 2004;232:560-4.
15. Bouros D, Wells AU, Nicholson AG, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med*. 2002;165:1581-6.
16. Goldin JG, Lynch DA, Strollo DC, et al. High-resolution CT scan finding in patients with symptomatic scleroderma-related interstitial lung disease. *Chest*. 2008;134:358-67.
17. Goh NS, Desai SR, Veeraraghaven S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med*. 2008;177:1248-54.
18. Gargani L, Doveri M, D'Errico L, et al. Ultrasound lung comets in systemic sclerosis: a chest sonography hallmark of pulmonary interstitial fibrosis. *Radiology (Oxford)*. 2009;48:1382-7.
19. Clements PJ, Goldin JG, Kleerup EC, et al. Regional differences in bronchoalveolar lavage and thoracic high-resolution computed tomography results in dyspnoic patients with systemic sclerosis. *Arthritis Rheum*. 2004;50:1909-17.
20. Goh NS, Veeraraghaven S, Desai SR, et al. Bronchoalveolar lavage cellular profiles in patients with systemic sclerosis-associated interstitial lung disease are not predictive of disease progression. *Arthritis Rheum*. 2007;56:2005-12.
21. Strange C, Bolster MB, Roth ND, et al. Bronchoalveolar lavage and response to cyclophosphamide in scleroderma interstitial lung disease. *Am J Respir Crit Care Med*. 2008;177:91-8.
22. Kowal-Bielecka O, Kowal K, Highland KB, et al. Bronchoalveolar lavage fluid in scleroderma interstitial lung disease: Technical aspects and clinical correlations: review of the literature. *Semin Arthritis Rheum*. 2010;40:73-88.
23. Kim DS, Yoo B, Lee JS, et al. The major histopathologic pattern of pulmonary fibrosis in scleroderma is nonspecific interstitial pneumonia. *Sarc Vasc Diffuse Lung Dis*. 2002;19:121-7.
24. Taylor JG, Bolster MB. Bronchiolitis obliterans with organizing pneumonia associated with scleroderma and scleroderma spectrum diseases. *J Clin Rheumatol*. 2003;9:239-45.
25. Chaer RA, Massad MG, Evans A, et al. Systemic sclerosis complicated by diffuse alveolar hemorrhage. *Med Sci Monit*. 2001;7:1013-5.

26. Furst DE, Clements PJ. D-penicillamine is not an effective treatment in systemic sclerosis. *Scand J Rheumatol*. 2001;30:189-91.
27. Donald P, Tashkin DP, Elashoff R, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med*. 2006;354:2655-66.
28. Available from www.pneumotox.com [accessed April 2010].
29. Segura A, Yuste A, Cercos A, et al. Pulmopnary fibrosis induced by cycliphosphamide. *An Pharmacother*. 2001;35:894-7.
30. Yiannopoulos G, Pastromas V, Antonopoulis I, et al. Combination of intravenous pulses of cyclophosphamide and methylpredniolon in patients with systemic sclerosis and interstitial lung disease. *Rheumatol Int*. 2007;27:357-61.
31. Liossia SN, Bounas A, Andonopoulos AP. Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease. *Rheumatology (Oxford)*. 2006;45:1005-8.
32. Derk CT, Grace E, Shenin M, et al. A prospective open-label study of mycophenolate mofetil for the treatment of diffuse systemic sclerosis. *Rheumatology (Oxford)*. 2009;48:1595-9.
33. Quillinan NP, Denton CP. Disease-modifying treatment in systemic sclerosis: current status. *Curr Opin Rheumatol*. 2009;21:636-41.
34. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum*. 2006;54:3962-70.
35. Saggar R, Khanna D, Furst DE, et al. Systemic sclerosis and bilateral lung transplantation: a single center experience. *Eur Respir J*. 2010;36:893-900.
36. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum*. 2000;43:2437-44.
37. Williams MH, Das C, Handler CE, et al. Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. *Heart*. 2006;92:926-32.
38. Mukerjee D, St George D, Coleiro B, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis*. 2003;62:1088-93.
39. Kumar U, Ramteke R, Yadav R, et al. Prevalence and predictors of pulmonary artery hypertension in systemic sclerosis. *J Assoc Physicians India*. 2008;56:413-7.
40. Chang B, Shachna L, White B, et al. Natural history of mild-moderate pulmonary hypertension and risk factors for severe pulmonary hypertension in scleroderma. *J Rheumatol*. 2006;33: 269-74.
41. Mathai SC, Bueso M, Hummers LK, et al. Disproportionate elevation of N-terminal pro-brain natriuretic peptide in scleroderma-related pulmonary hypertension. *Eur Respir J*. 2010;35: 95-104.
42. Allanore Y, Borderie D, Avouac J, et al. High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. *Arthritis Rheum*. 2008;58:284-91.
43. Proudman SM, Stevensen WM, Sahhar J, Celermajer D, et al. Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. *Intern Med J*. 2007;37: 485-95.
44. Denton CP, Humbert M, Rubin L, et al. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease; a subgroup analysis of the pivotal clinical trials and their open-label extensions. *Ann Rheum Dis*. 2006;65:1336-40.

45. de Oliveira NC, dos Santos Sabbag LM, Ueno LM, et al. Reduced exercise capacity in systemic sclerosis patients without pulmonary involvement. *Scand J Rheumatol*. 2007;36:458-61.

46. Schoindre Y, Meune C, Dinh-Xuan AT, et al. Lack of specificity of the 6-minute walk test as an outcome measure for patients with systemic sclerosis. *J Rheumatol*. 2009;36:1481-5.

47. Galie`N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J*. 2004;25:2243-78.

48. Sanchez-Roman J, Opitz CF, Kowal-Bielecka O, et al. Screening for PAH in patients with systemic sclerosis: focus on Doppler echocardiography. *Rheumatology (Oxford)*. 2008;47: 33-5.

49. Vonk MC, Sander MH, van den Hoogan FH, et al. Right ventricle Tei-index: a tool to increase the accuracy of non-invasive detection of pulmonary arterial hypertension in connective tissue disease. *Eur J Echocardiogr*. 2007;8:317-21.

50. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med*. 2003;167: 735-40.

51. Savino G, Zwerner P, Herzog C, et al. CT of cardiac function. *J Thorac Imaging*. 2007;22: 86-100.

52. Tan RT, Kuzo R, Goodman LR, et al. Utility of CT scan evaluation for predicting pulmonary hypertension in patients with parenchymal lung disease. *Chest*. 1998;113:1250-6.

53. Edwards PD, Bull RK, Coulden R. CT measurement of main pulmonary artery diameter. *Br J Radiol*. 1998;71:1018-20.

54. Ng CS, Wells AU, Padley SP. CT signs of chronic pulmonary arterial hypertension: the ratio of main pulmonary artery to aortic diameter. *J Thorac Imaging*. 1999;14:270-8.

55. Devaraj A, Hansell DM. Computed tomography signs of pulmonary hypertension: old and new observations. *Clin Radiology*. 2009;64:751-60.

56. Devaraj A, Wells AU, Meister MG, et al. Detection of pulmonary hypertension with multidetector CT and echocardiography alone and in combination. *Radiology*. 2010;254: 609-16.

57. Seibold JR. International Scleroderma Network Newsletter. 2007 Sept 30.

58. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med*. 2000;132:435-4.

59. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346:896-903.

60. Galie N, Hoeper MM, Jamsa P, et al. Bosentan improves hemodynamics and delays time to clinical worsening in patients with mild symptomatic pulmonary arterial hypertension: results of the EARLY study. *Eur Heart J*. 2007;28:140.

61. Barst RJ, Langleban D, Badesch D, et al. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxentan. *J Am Coll Cardiol*. 2006;47:2049-56.

62. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;353:2148-57.

63. Wells AU, du Bois RM. Bronchiolitis in association with connective tissue disorders. *Clin Chest Med*. 1993;14:655-66.

64. Bhalla M, Silver RM, Shepard JA, et al. Chest CT in patients with scleroderma: prevalence of asymptomatic esophageal dilatation and mediastinal lymphadenopathy. *Am J Roentdgenol*. 1993;161:269-72.

65. Ntoumazios SK, Voulgari PV, Potsis K, et al. Esophageal involvement in scleroderma: gastroesophageal reflux, the common problem. *Semin Arthritis Rheum*. 2006;36:173-81.
66. Savarino E, Bazzica M, Zentilin P, et al. Gastroesophageal reflux and pulmonary fibrosis in scleroderma: a study using pH-impedance monitoring. *Am Rev Respir Crit Care Med*. 2009;179:408-13.
67. Wooten M. Systemic sclerosis and malignancy: a review of the literature. *South Med J*. 2008;101:59-62.
68. Ong VH, Denton CP. Innovative therapies for systemic sclerosis. *Curr Opin Rheumatol*. 2010;22:264-72.
69. Miossec P, Kom T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. *N Engl J Med*. 2009;361:888-98.
70. Sundrud MS, Koralov SB, Feuerer M, et al. Halofuginone inhibits Th17 cells differentiation by activating the amino acid starvation response. *Science*. 2009;324:1334-8.
71. Daoussis D, Liossis SN, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from 1-year, proof-of-principle study. *Rheumatology (Oxford)*. 2010;49:271-80.
72. Vonk MC, Marjanovic Z, van den Hoogen FH, et al. Long-term follow-up results after autologous hemapoietic stem-cell transplantation for severe systemic sclerosis. *Ann Rheum Dis*. 2008;67:98-104.
73. Akhmethshina A, Venalis P, Dees C, et al. Treatment with imatinib prevents fibrosis in different preclinical models of systemic sclerosis and induces regression of established fibrosis. *Arthritis Rheum*. 2009;60:219-24.
74. Distler JH, Distler O. Tyrosine kinase inhibitors for the treatment of fibrotic diseases such as systemic sclerosis: towards molecular targeted therapies. *Ann Rheum Dis*. 2010;69:i48-51.
75. Shi-wen X, Eastwood M, Stratton RJ, et al. Rosiglitazone alleviates the persistent fibrotic phenotype of lesional skin scleroderma fibroblasts. *Rheumatology (Oxford)*. 2010;49:259-63.
76. Abou-Raya A, Abou-Raya S, Helmi M. Statins: potentially useful in therapy of systemic sclerosis-realted Raynaud's phenomenon and digital ulcers. *J Rheumatol*. 2008;35:1801-8.