

# Scleroderma Lung Disease – Other Lung Complications in Systemic Sclerosis

Maria do Socorro Teixeira Moreira Almeida

Department of General Practice, Federal University of Piauí, Brazil

## Abstract

Scleroderma or systemic sclerosis (SSc) is a clinically heterogeneous, multi-system autoimmune disorder characterized by endothelial dysfunction, dysregulation of fibroblasts resulting in excessive production of collagen and profound abnormalities of the immune system. Pulmonary involvement is common and occurs in all SSc subsets, including limited cutaneous systemic sclerosis, diffuse cutaneous systemic sclerosis and SSC sine scleroderma. Aside from the common complications of pulmonary vasculopathy and interstitial lung disease (ILD), other less frequent pulmonary complications have been reported in SSc. The emphasis of this review will be on other lung complications in systemic sclerosis.

**Keywords:** Systemic sclerosis; Scleroderma lung disease

## Introduction

Scleroderma or systemic sclerosis (SSc) is a heterogeneous disorder characterized by endothelial dysfunction, dysregulation of fibroblasts resulting in excessive production of collagen and profound abnormalities of the immune system. These changes cause progressive fibrosis of the skin and internal organs, system failure and death [1]. Patients with SSc may exhibit proliferative small artery and obliterative microvascular disease, plus inflammation and fibrosis affecting the skin, oesophagus, respiratory tract and other target organs [2]. Pulmonary involvement is second in frequency only to oesophagus involvement as a visceral complication of systemic sclerosis and has surpassed renal involvement as the most common cause of death. Interstitial lung disease (ILD) and pulmonary vascular disease, particularly pulmonary arterial hypertension (PAH), are the most commonly encountered types of lung involvement [3]. Mortality from scleroderma renal crisis has been significantly reduced with the use of angiotensin converting enzyme inhibitors beginning in the 1980s and lung disease has emerged as the leading cause of mortality. Pulmonary involvement is common and occurs in all SSc subsets, including limited cutaneous systemic sclerosis (lcSSc, formerly CREST syndrome, syndrome consisting of calcinosis cutis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and telangiectasia), diffuse cutaneous systemic sclerosis (dcSSc, formerly progressive systemic scleroderma) and SSc sine scleroderma [4]. Patients with lcSSc have skin involvement distal to the elbows and knees, whereas patients with dcSSc have truncal involvement and more proximal limb involvement. The face may be affected in lcSSc and dcSSc. ILD and pulmonary arterial hypertension (PAH) are now the leading causes of mortality in SSc [5]. The risks for severe pulmonary manifestation are the following: male sex, diffuse SSc, presence of antitopoisomerase antibodies and inflammatory signs and significantly reduced diffusion capacity. Progression of lung disease in SSc is variable and difficult to predict. However, pulmonary function measures early in the disease process may predict, in ILD, progression and mortality. Differentiation between ILD, PAH and other causes of dyspnoea in patients with SSc, can be clinically difficult. However, the identification and staging of pulmonary manifestation is of paramount importance to the management of patients [2].

## Manifestations of SSc in the Respiratory System [4]

### 1. ILD

Nonspecific interstitial pneumonia (NSIP)

\_ Usual interstitial pneumonia (UIP)

\_ Diffuse alveolar damage (DAD)

\_ Cryptogenic organizing pneumonia (COP)

2. Pulmonary hypertension

3. Pleural involvement

4. Aspiration pneumonia

5. Alveolar hemorrhage

6. Small airways disease

7. Malignancy

8. Respiratory muscle weakness

9. Drug-induced toxicity

10. Spontaneous pneumothorax

11. Pneumoconiosis (silicosis)

## Other Lung Complications in Systemic Sclerosis

Aside from the common complications of pulmonary vasculopathy and ILD, other less frequent pulmonary complications have been reported in SSc. An occasional obstructive ventilator defect has been observed in non smoker connective tissue disease (CTD) (including SSc) patients [6]. Pleural effusions, perhaps related to serositis [7,8] and spontaneous pneumothorax [9,10] have been in the context of ILD. Several large studies have found a high prevalence of lung cancer in SSc patients [11,12]. These patients are typically female with underlying ILD. The histological types of malignancy include bronchoalveolar carcinomas and adenocarcinomas [13], tumors less likely to be associated with a history of cigarette smoking [14]. However, a recent large population-based cohort study has questioned the link between

**\*Corresponding author:** Maria do Socorro Teixeira Moreira Almeida, Professor of Rheumatology, Federal University of Piauí, Avenida João Tajar Elias, CEP 64.049-300, Brazil, Tel: 55-86-32324390; E-mail: [esteios@uol.com.br](mailto:esteios@uol.com.br)

**Received** November 10, 2011; **Accepted** February 17, 2012; **Published** February 20, 2012

**Citation:** Almeida MSTM (2012) Scleroderma Lung Disease – Other Lung Complications in Systemic Sclerosis. *Rheumatology* S1:009. doi:10.4172/2161-1149.S1-009

**Copyright:** © 2012 Almeida MSTM. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

SSc and lung cancer [15]. Finally, myopathy and myositis in the context of an overlap syndrome are not uncommon complications of SSc and may cause respiratory muscle dysfunction [16]. The emphasis of this review will be on other lung complications in systemic sclerosis.

### **Pleural involvement**

Pleural disease occurs in SSc as a result of pleural effusions or fibrosis. Pleural effusions are uncommon in scleroderma in the absence of clinical congestive heart failure or interstitial lung disease, but have been reported in 15% of patients with an overlap syndrome and scleroderma [7]. Thompson and Pope [7] observed a few patients in his scleroderma population with significant pleural effusions that were not explained by other aetiologies. They hypothesized that pleural effusion may actually be more common than reported by previous literature and may be more prevalent in patients with diffuse compared to limited disease. Upon testing this hypothesis and excluding the index cases, his prospective case-control study found the presence of a pleural effusion in only one out of the 37 study patients, which is consistent with previous literature. The patient with the pleural effusion did have diffuse scleroderma. His chart review provided three additional pleural effusions in 21 patients with chest radiographs and thus 7% (4/58) of patients in his cohort had pleural effusions and this was more frequent in diffuse scleroderma. The pathogenesis of pleural effusion in SSc is unknown, but may relate to vasculitis of the pleura, concomitant heart failure and infection. The characteristics of the pleural fluid have not been well defined, although one study noted a high level of CA125 in pleural fluid and serum [17]. A rare case with SSc accompanied by massive pleural effusion was presented by Funauchi et al. [18], in which the serum CA 125 level paralleled the change of the pleural effusion. Elevation of CA125 in the serum and pleural fluid was thought important for differential diagnosis of malignancy and pleuritis complicated by collagen diseases including SSc. Furthermore, CA125 may be an indicator of the activity of serositis in collagen vascular diseases [18].

### **Aspiration pneumonia**

Aspiration pneumonia occurs when vomitus or reflux gets into the lungs, causing an often deadly form of pneumonia. Anyone (with or without scleroderma) can get aspiration pneumonia. It often occurs in systemic scleroderma patients due to esophagus problems, as esophageal dysmotility and an incompetent lower esophageal sphincter.

Does chronic microaspiration cause idiopathic pulmonary fibrosis? Emerging data support a role of chronic microaspiration (i.e., subclinical aspiration of small droplets) in the pathogenesis and natural history of idiopathic pulmonary fibrosis. However, the precise relationship between chronic microaspiration and idiopathic pulmonary fibrosis remains unknown [19]. Symptoms include cough, coughing up sputum and sometimes fever. The pneumonia will usually show up on chest x-ray, but a sputum culture will show that the pneumonia isn't caused by bacteria. Aspiration pneumonia should be suspected if a scleroderma patient has recurrent pneumonia, especially if there is an overlap or related myositis that might increase the risk for aspiration [20]. As estimated 30-50% of cases lead to death. However, mild cases may cause no symptoms at all. Preventive measures include carefully following instructions for dealing with reflux (heartburn), such as taking medicines, elevating the head of the bed and not eating near bedtime. Aggressive antireflux treatment may be helpful to reduce pulmonary damage caused by aspiration in patients with SSc, because a direct correlation has been shown between reflux severity and PF severity [21]. Another more recent study emphasized the need for

larger controlled studies to evaluate whether development of SSc-ILD can be prevented by preventing reflux [22].

### **Alveolar hemorrhage**

Some types of pulmonary involvement are resistant to currently available treatment regimens and thus considered as intractable conditions. These include acute/subacute interstitial pneumonia in dermatomyositis, pulmonary interstitial fibrosis in scleroderma and diffuse alveolar hemorrhage [23]. Pulmonary hemorrhage with acute renal failure and diffuse alveolar hemorrhage in the absence of history of renal involvement or penicillamine intake rarely been reported in patients with systemic sclerosis [2]. There are some relates of patients with systemic sclerosis and diffuse alveolar hemorrhage [24-27], some cases in pulmonary-renal syndrome [28]. There are accumulating evidences showing the effectiveness of cyclophosphamide in patients with this intractable condition, especially those with active alveolitis [23]; Chaer et al. [27] emphasized the importance of steroid therapy for treatment of alveolar hemorrhage.

### **Small airways disease**

Obstructive disease involving peripheral airways has been noted in diffuse interstitial pulmonary disease, including sarcoidosis and cryptogenic fibrosing alveolitis. The possibility of obstruction of small airways in systemic sclerosis has been suggested by widespread bronchiolectasis and peribronchial fibrosis noted at necropsy. Findings suggests that diffuse interstitial pulmonary disease due to SSc generally does not lead to functional evidence of obstruction in peripheral airways and that the latter is found it can likely be attributed to the effects of concomitant cigarette smoking [29]. To evaluate small airways dysfunction (SAD) in a pure systemic sclerosis population, Kostapoulos et al. [30] performed pulmonary function studies in 31 nonsmoking patients and 31 age- and sex-matched nonsmoking control subjects. Patients' FVC (forced vital capacity), TLC (total lung capacity) and Dco (diffusing capacity for CO) mean values were significantly lower compared with the corresponding values of the controls ( $p < 0.05$ ), while there was no difference in MEF25 (maximum expiratory flow at 25 percent of vital capacity), 1W and RV/TLC (residual volume/total lung capacity). Seven (22.6 percent) of 31 patients and four controls (a nonsignificant difference) had evidence of SAD, namely a MEF25 less than 60 percent of predicted. Positive correlation ( $p < 0.001$ ) was found between MEF25 and FEV1/FVC (forced expiratory volume in 1 sec / forced vital capacity) in the patients. Moreover, no differences were found in abnormal lung function patients with and those without SAD in demographic, clinical, roentgenologic and serologic features and results of pulmonary function tests. These findings suggest that SAD in our patients is not a characteristic and early manifestation of systemic sclerosis and that, when present, it is not correlated with the severity of the pulmonary involvement in scleroderma. In other study [31], lung volumes, forced expiratory flow-volume curves, diffusing capacity indexes and arterial blood gases were measured in 72 non-smoking patients with various connective tissue diseases. Small airways disease and a diffusion capacity impairment were the most frequent and marked functional abnormalities in the whole group and were often present in asymptomatic patients. Different lung function defects seemed to be present in each disease group. In fact, large airway obstruction was prevalent in progressive systemic sclerosis, diffusion capacity impairment in systemic lupus erythematosus and small airways disease in rheumatoid arthritis. In contrast, primary Sjögren's syndrome appeared to be the connective tissue disease in which lung function abnormalities were less frequent and less pronounced.

## Malignancy

Malignancy is associated with systemic sclerosis, both the limited and diffuse forms, in 3.6 to 10.7%. The diagnosis of systemic sclerosis may occur before, concurrent with, or after the diagnosis of malignancy. Risk factors for the development of malignancy in patients with systemic sclerosis are female gender, increased age and diffuse systemic sclerosis [32]. A variety of mechanisms have been postulated in systemic sclerosis patients that predispose them to malignancy: defects in immune surveillance, impaired clearance of cardiogens, increased susceptibility to malignant transformation due to epithelial hyperplasia, inflammatory secretion of reactive oxygen radicals and familial susceptibility. Many studies have reported an increased frequency of neoplasm in patients with SSc, with lung carcinoma, especially bronchoalveolar carcinoma, being the most common [33]. In the Pittsburgh cohort, 14 of 262 (5%) patients with SSc developed a malignancy and an increase in lung cancer was observed in the setting of chronic PF even in the absence of tobacco use [14]. In a study by Peters-Golden and colleagues [33], 71 patients with SSc were followed for a mean of 5 years and 3 cases of lung cancer were observed with 8.6 cases/1000 persons/y post hoc incidence of lung cancer. This compared with an expected incidence ratio of 0.52 cases/1000 persons/y, leading them to calculate a relative risk ratio for lung cancer in SSc of 16.5. Each of the 3 cases of lung cancer had radiographic evidence of pulmonary fibrosis (PF), but no definite association with tobacco use [34]. Recurrent cellular injury, genetic damage to local epithelial cells and frequent use of immunosuppressive drugs are believed to be predisposing factor to the development of cancer in the setting of SSc [3]. Because neoplasm may occur before, during, or years after the diagnosis of SSc, patients should be monitored for this, especially if they receive immunosuppression, or when they present with hemoptysis [20].

## Respiratory muscle weakness

Respiratory compromise can occur in systemic sclerosis solely on the basis of restriction in chest wall expansion in the absence of intrinsic lung disease and that this may have serious consequences. Respiratory muscle weakness with hypercapnic respiratory failure in systemic sclerosis has rarely been described in the literature, but the prevalence and mechanism of this have not been well characterized. In one previously reported case, chest wall infiltration from systemic sclerosis resulted in hypercapnic respiratory failure; in another reported case, a patient with systemic sclerosis developed hypercapnic respiratory failure secondary to severe ventilatory muscle weakness from a presumed myopathy of the respiratory muscles [35]. Shrinking lung syndrome usually manifest in dyspnea, decreased lung volume associated with elevated diaphragm. Shrinking lung syndrome is rare but must be considered in patients with autoimmune disease and dyspnea. The diagnosis can be difficult because of clinical, pathological and functional features with are controversial [36].

## Drug-induced toxicity

Certain strong medicines may have the undesirable side effect of causing pulmonary fibrosis. Some of them are: nitrofurantoin (sometimes used for urinary tract infections), amiodarone (sometimes prescribed for an irregular heart rate), bleomycin, cyclophosphamide and methotrexate (sometimes prescribed to fight cancer). Patients of any age with tuberculosis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and others diseases and conditions, or with exposure to any of the drugs listed above, may develop pulmonary fibrosis, but this is rare. Patients who develop idiopathic pulmonary fibrosis are usually middle-aged men and women and there appears

to be no sexual, racial or geographical tendency. People who smoke or who are former smokers are more likely to develop pulmonary fibrosis than people who have never smoked. D-Penicillamine has long been used to treat SSc, although its use is not supported by the results of a randomized trial comparing low and high doses [37]. This drug has been associated with bronchiolitis obliterans and Goodpasture syndrome. Other medications used in the treatment of SSc-ILD including the standard of care therapy at this time, cyclophosphamide (CYC) have been associated with pulmonary toxicity. CYC-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 [38].

## Spontaneous pneumothorax

Spontaneous pneumothorax has been reported, often in association with subpleural blebs in the context of interstitial lung disease (ILD). Interstitial fibrosis is not an essential underlying condition for the development of pneumomediastinum, as some cases with pneumomediastinum reported in the literature had no findings of interstitial lung disease. Rupture of the alveoli or honeycomb cysts and subsequent air leakage into the surrounding interstitium could be regarded as the cause of pneumomediastinum in patients with pulmonary fibrosis; honeycombing and violent cough were considered to be predisposing factors to the rupture [10].

## Pneumoconiosis (silicosis)

Occupational exposure to crystalline silica dust has been examined as a possible risk factor with respect to several systemic autoimmune diseases, including rheumatoid arthritis, scleroderma, lupus and some of the small vessel vasculitides with renal involvement (e.g., microscopic polyangiitis, Wegener's granulomatosis) [39]. 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 [40]. Patients with silicosis in general are also noted to have alterations in immunity, with a recent article noting alterations in soluble interleukin 2 (sIL2) receptors in these patients [41]. The mechanisms for the biological effects of silica are still not fully understood. Crystalline silica may act as an immunoadjuvant. When phagocytized by macrophages silica particles cause the release of inflammatory mediators that activate more macrophages and lymphocytes, which in turn increase the production of matrix metalloproteinase enzymes involved in the degradation and remodeling of extracellular matrix. Another proposed mechanism is that silica causes defective apoptosis leading to the prolonged survival of pathogenic lymphocytes and the development of silica-associated systemic lupus. Silica exposure may theoretically be linked to other environmental exposures that may themselves be related to the increased possibility of developing CTD. For example, smoking in conjunction with silica exposure has been reported to be a risk factor for the development of radiographic changes of silicosis [42] and smoking has been reported to be a risk factor for the development of CTD, particularly rheumatoid arthritis (RA) [43]. Smoking has been identified to interact with certain susceptibility genes in the host to trigger a cascade of immuno-inflammatory events leading to anti-CCP positive RA. Silica-exposure could be playing a similar role; and this potential needs to be investigated. The link between respirable silica exposure and autoimmune disease may have some bearing on the possible association between silicone breast implants and autoimmune disease, although the nature of the silica involved is quite different in two situations [44].



## Conclusion

Pulmonary complications are common in SSc and, in the case of SSc-ILD and SSc-PAH, the leading causes of death. Exertional dyspnea and dry cough are the most common presenting symptoms in patients with SSc who develop pulmonary involvement. However, dyspnea may have many causes in patients with SSc and all SSc patients (with or without dyspnea) should be thoroughly evaluated for the presence of lung involvement, regardless of their characterization as either lcSSc or dcSSc. Unfortunately, systemic sclerosis lung disease is often not detected or diagnosed until the late stages, particularly in those who did not develop the classic signs of skin-hardening or sclerodactyly, or those who only exhibited subtle respiratory symptoms.

## References

1. M Hassoun P (2011) Lung involvement in systemic sclerosis. *Presse Med* 40: e3-e17.
2. Wells AU, Steen V, Valentini G (2009) Pulmonary complications: one of the most challenging complications of systemic sclerosis. *Rheumatology (Oxford)* 3: iii40-iii44.
3. Le Pavec J, Launay D, Mathai SC, Hassoun PM, Humbert M (2011) Scleroderma lung disease. *Clin Rev Allergy Immunol* 40: 104-116.
4. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, et al. (1988) Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 15: 202-205.
5. Steen VD, Medsger TA (2007) Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 66: 940-944.
6. Kim EA, Lee KS, Johkoh T, Kim TS, Suh GY, et al. (2002) Interstitial lung diseases associated with collagen vascular diseases: radiologic and histopathologic findings. *Radiographics* 22: S151-S165.
7. Thompson AE, Pope JE (1998) A study of the frequency of pericardial and pleural effusions in scleroderma. *Br J Rheumatol* 37: 1320-1323.
8. Taormina VJ, Miller WT, Gefter WB, Epstein DM (1981) Progressive systemic sclerosis subgroups: variable pulmonary features. *AJR Am J Roentgenol* 137: 277-285.
9. Lang B, Ortlieb H, Meske S, Hauke G, Peter HH (1989) Progressive systemic sclerosis presenting with spontaneous pneumothorax. *J Rheumatol* 16: 254-256.
10. Teixeira Moreira Almeida Mdo S, Dias LT, Fernandes SJ, Almeida JV (2007) Spontaneous pneumomediastinum and subcutaneous emphysema in systemic sclerosis. *Rheumatol Int* 27: 675-677.
11. Hill CL, Nguyen AM, Roder D, Roberts-Thomson P (2003) Risk of cancer in patients with scleroderma: a population based cohort study. *Ann Rheum Dis* 62: 728-731.
12. Rosenthal AK, McLaughlin JK, Linet MS, Persson I (1993) Scleroderma and malignancy: an epidemiological study. *Ann Rheum Dis* 52: 531-533.
13. Yang Y, Fujita J, Tokuda M, Bandoh S, Ishida T (2001) Lung cancer associated with several connective tissue diseases: with a review of literature. *Rheumatol Int* 21: 106-111.
14. Roumm AD, Medsger TA Jr (1985) Cancer and systemic sclerosis. An epidemiologic study. *Arthritis Rheum* 28: 1336-1340.
15. Chatterjee S, Dombi GW, Severson RK, Mayes MD (2005) Risk of malignancy in scleroderma: a population-based cohort study. *Arthritis Rheum* 52: 2415-2424.
16. Olsen NJ, King LE Jr, Park JH (1996) Muscle abnormalities in scleroderma. *Rheum Dis Clin North Am* 22: 783-796.
17. Highland KB, Heffner JE (2004) Pleural effusion in interstitial lung disease. *Curr Opin Pulm Med* 10: 390-396.
18. Funachi M, Ikoma S, Yu H, Sugiyama M, Ohno M, et al. (2000) A case of progressive systemic sclerosis complicated by massive pleural effusion with elevated CA125. *Lupus* 9: 382-385.
19. Lee JS, Collard HR, Raghu G, Sweet MP, Hays SR, et al. (2010) Does chronic microaspiration cause idiopathic pulmonary fibrosis? *Am J Med* 123: 304-311.
20. Hant FN, Herpel LB, Silver RM (2010) Pulmonary manifestations of scleroderma and mixed connective tissue disease. *Clin Chest Med* 31: 433-449.
21. Johnson DA, Drane WE, Curran J, Cattau EL Jr, Ciarleglio C, et al. (1989) Pulmonary disease in progressive systemic sclerosis. A complication of gastroesophageal reflux and occult aspiration? *Arch Intern Med* 149: 589-593.
22. Savarino E, Ghio M, Marabotto E, Zentilin P, Sammito G, et al. (2009) Possible connection between gastroesophageal reflux and interstitial pulmonary fibrosis in patients with systemic sclerosis. *Recenti Prog Med* 100: 512-516.
23. Kuwana M (2004) Collagen diseases with pulmonary involvement. *Nihon Rinsho Meneki Gakkai Kaishi* 27: 118-126.
24. Shoda T, Kotani T, Takeuchi T, Makino S, Hanafusa T (2009) A fulminant case of systemic sclerosis/dermatomyositis complicating thrombotic microangiopathy and diffuse alveolar hemorrhage. *Nihon Kokyuki Gakkai Zasshi* 47: 227-231.
25. Yamada T, Nakajima H, Tanaka E, Nakajima A, Terai C, et al. (2003) Case of systemic sclerosis presenting with alveolar hemorrhage and positive anti-neutrophil cytoplasmic myeloperoxidase antibody (MPO-ANCA) without pathological renal involvement. *Ryumachi* 43: 690-695.
26. Toyoshima M, Chida K, Enomoto N, Nakamura Y, Imokawa S, et al. (2005) A case of diffuse alveolar hemorrhage associated with interstitial pneumonia and systemic sclerosis. *Nihon Kokyuki Gakkai Zasshi* 43: 437-441.
27. Chaer RA, Massad MG, Evans A, Olopade C, Varga J (2001) Systemic sclerosis complicated by diffuse alveolar hemorrhage. *Med Sci Monit* 7: 1013-1015.
28. Defendenti C, Spina MF, Castiglione A, Atzeni F, Miadonna A, et al. (2009) Alveolar hemorrhage in pulmonary-renal syndrome anti-SCL/70 and anti-MPO-ANCA positive. *Recenti Prog Med* 100: 361-364.
29. Bjerke RD, Tashkin DP, Clements PJ, Chopra SK, Gong H Jr, et al. (1979) Small airways in progressive systemic sclerosis (PSS). *Am J Med* 66: 201-209.
30. Kostopoulos C, Rassidakis A, Sfikakis PP, Antoniadis L, Mavrikakis M (1992) Small airways dysfunction in systemic sclerosis. A controlled study. *Chest* 102: 875-881.
31. Vitali C, Viegi G, Tassoni S, Tavoni A, Paoletti P, et al. (1986) Lung function abnormalities in different connective tissue diseases. *Clin Rheumatol* 5: 181-188.
32. Wooten M (2008) Systemic sclerosis and malignancy: a review of the literature. *South Med J* 101: 59-62.
33. Talbott JH, Barrocas M (1980) Carcinoma of the lung in progressive systemic sclerosis: a tabular review of the literature and a detailed report of the roentgenographic changes in two cases. *Semin Arthritis Rheum* 9: 191-217.
34. Peters-Golden M, Wise RA, Hochberg M, Stevens MB, Wigley FM (1985) Incidence of lung cancer in systemic sclerosis. *J Rheumatol* 12: 1136-1139.
35. Pugazhenti M, Cooper D, Ratnakant BS, Postlethwaite A, Carbone L (2003) Hypercapnic respiratory failure in systemic sclerosis. *J Clin Rheumatol* 9: 43-46.
36. Branger S, Schleinitz N, Gayet S, Veit V, Kaplanski G, et al. (2004) Shrinking lung syndrome and systemic auto-immune disease. *Rev Med Interne* 25: 83-90.
37. Clements PJ, Furst DE, Wong WK, Mayes M, White B, et al. (1999) High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double-blind, randomized, controlled clinical trial. *Arthritis Rheum* 42: 1194-1203.
38. Malik SW, Myers JL, DeRemee RA, Specks U (1996) Lung toxicity associated with cyclophosphamide use. Two distinct patterns. *Am J Respir Crit Care Med* 154: 1851-1856.
39. Parks CG, Conrad K, Cooper GS (1999) Occupational exposure to crystalline silica and autoimmune disease. *Environ Health Perspect* 5: 793-802.
40. Ajlani H, Meddeb N, Sahli H, Sellami S (2009) Erasmus syndrome: case report. *Rev Pneumol Clin* 65: 16-22.
41. Hayashi H, Maeda M, Murakami S, Kumagai N, Chen Y, et al. (2009) Soluble interleukin-2 receptor as an indicator of immunological disturbance found in silicosis patients. *Int J Immunopathol Pharmacol* 22: 53-62.
42. Rosenman KD, Reilly MJ, Rice C, Hertzberg V, Tseng CY, et al. (1996) Silicosis among foundry workers. Implication for the need to revise the OSHA standard. *Am J Epidemiol* 144: 890-900.

- 
43. Pedersen M, Jacobsen S, Garred P, Madsen HO, Klarlund M, et al. (2007) Strong combined gene-environment effects in anti-cyclic citrullinated peptide-positive rheumatoid arthritis: a nationwide case-control study in Denmark. *Arthritis Rheum* 56: 1446-1453.
44. Steenland K, Goldsmith DF (1995) Silica exposure and autoimmune diseases. *Am J Ind Med* 28: 603-608.

This article was originally published in a special issue, [Lung Involvement in Scleroderma](#) handled by Editor(s). Dr. Galina Bogatkevich, Medical University of South Carolina, USA