Autoimmunity Reviews 15 (2016) 1094–1108

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

# Pulmonary involvement in systemic sclerosis

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ARTICLE INFO

Available online 4 August 2016

*Keywords:*
Systemic sclerosis
Pulmonary involvement
Radiology
Tomography
X-ray computed
Pathology

ABSTRACT

Systemic sclerosis (SSc) is a multi-systemic autoimmune disease that mainly affects the skin, lungs, gastrointestinal tract, heart and kidneys. Pulmonary disease in patients with SSc is strongly associated with mortality. The mechanisms involved into its pathophysiology include the activation of autoimmune cells and hyperplasia of fibroblasts with an increased capacity to produce collagen and diminished collagen breakdown. Although pulmonary biopsy is the gold standard for the diagnosis of interstitial lung disease in SSc, the most commonly used method is high-resolution computed tomography due to its high sensitivity and specificity. Herein, a comprehensive review on the pulmonary involvement in SSc is presented highlighting the radiologic–pathologic correlations.

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**Contents**



*Abbreviations:* AECA, anti-endothelial cell antibodies; AD, autoimmune disease; APRIL, proliferation-inducing ligand; a-SMA, alfa smooth muscle actin; BAFF, factor B-cell activating factor; BAL, broncoalveolar lavage; CH, capillary hemangiomatosis; DAD, diffuse alveolar damage; dcSSc, diffuse cutaneous systemic sclerosis; DLco, carbon monoxide diffusion capacity; ELAM-1, endothelium leukocyte adhesion molecule 1; FVC, forced vital capacity; HRCT, high resolution computed tomography; ICAM-1, intercellular adhesion molecule 1; IGF I, insulin-like growth factor 1; IL-1, interleukin 1; ILD, interstitial lung disease; KL-6, krebs von den lungen-6; lcSSc, limited cutaneous systemic sclerosis; MCP-1, monocyte chemoattractant protein-1; MMPs, metalloproteinases; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PDGF, platelets derived growth factor; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; RA, rheumatoid arthritis; ROS, reactive oxygen species; SP-D, surfactant protein D; SSc, systemic sclerosis; TGF-β, transforming growth factor beta; TIMPs, tissue inhibitors of metalloproteinases; TWEAK, TNF-like weak inducer of apoptosis; UIP, usual interstitial pneumonia; VCAM-1, vascular cell adhesion molecule 1.

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http://dx.doi.org/10.1016/j.autrev.2016.07.025
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## 1. Introduction

Systemic sclerosis (SSc) is a multifactorial, systemic autoimmune disease (AD) characterized by functional and structural damage to the microvasculature. The normal tissue architecture is destroyed by deposits of autoantibodies and collagen, resulting in fibrosis of skin and dysfunction of multiple organs [1–3].

Based on symptomatology and a physical exam, the following phenotypes have been established for the disease: a) limited cutaneous systemic sclerosis (lcSSc) (the distal cutaneous portion of the neck, elbows and knees are affected), b) diffuse cutaneous systemic sclerosis (dcSSc) (cutaneous areas of the neck, elbows and knees are affected proximally), c) systemic sclerosis *sine scleroderma* (vascular manifestations and serologic changes compatible with diffuse cutaneous scleroderma without cutaneous sclerosis) and d) polyautoimmunity (an additional coexisting AD) [3,4].

The organs affected in SSc include the skin, lungs, gastrointestinal tract (80%) [5], heart (pericardial effusion, arrhythmias, conduction defects, valve disease, myocardial ischemia, hypertrophic cardiomyopathy and heart failure) (15–35%) [6,7] and kidneys (5%) [8]. Since the 1980's, successful preventive treatment for renal crisis has made pulmonary complications the main cause of death [3,9].

Pulmonary disease in patients with SSc can be classified into two main groups, 1) primary pulmonary disease (i.e., lung parenchyma involvement and pulmonary hypertension) and 2) secondary pulmonary disease (i.e., airway illness due to bronco-aspiration that is secondary to gastro-oesophageal reflux, toxicity due to medications, and infections, among others) [9].

In order to explore the pulmonary involvement in SSc and its radiologic–pathologic correlations, a comprehensive review was conducted.

## 2. Materials and methods

### 2.1. Search strategy

A literature review focused on pulmonary involvement in systemic scleroderma was performed through the PubMed database and included articles in Spanish or English listed in PubMed up to December 2015. No limits regarding the publication type were included. The search was performed using the following Medical Subject Heading (MeSH) terms for SSc: “systemic sclerosis” and “scleroderma”, which were combined with MeSH terms and the following keywords referring to pulmonary involvement: “pulmonary involvement”, “interstitial lung disease”, “non-specific pneumonia”, “usual interstitial pneumonia”, “organizing pneumonia”, “combined emphysema and pulmonary fibrosis”, “diffuse alveolar damage”, “pulmonary hypertension”, “occlusive venous pulmonary disease”, “capillary haemangiomatosis”, “diffuse alveolar haemorrhage”, “airway disease”, “aspiration pneumonia”, “lipoid pneumonia”, “bronchiolocentric fibrosis” and “lung neoplasia”. Each term was cross-referenced for the greatest number of results.

A study was included if the following were true: a) the abstract was available; b) the study contained an original study, case report or case series; and c) the study reported patients diagnosed as SSc.

We hand-searched the bibliographies of all ultimately-included, full-text journal articles in order to identify any additional, relevant studies for inclusion in the review. The abstract and full texts articles were reviewed in the search of eligible studies. Duplicates were removed.

The radiological and histological images are illustrative and were obtained from the author's clinical records.

### 2.2. Results

There were 4009 articles identified in PubMed database. Of these, 381 papers were considered for eligibility. Eleven papers could not be found in full-text; therefore, data were extracted from the abstract. Finally, 94 articles fulfilling the eligibility criteria were included. Then, articles were classified into epidemiology, pathophysiology, biomarkers, clinical manifestations, diagnosis, histologic and radiologic patterns and treatment of pulmonary involvement in SSc.

## 3. Discussion

### 3.1. Pulmonary involvement in SSc

Pulmonary involvement in SSc is summarized in Table 1 [9,10]. The prevalence of interstitial lung disease (ILD) in SSc patients varies depending on the diagnostic method. In a series of autopsies, 100% of the SSc cases presented with ILD [11–13]. By high resolution computed tomography (HRCT), this condition was observed in up to 90% of cases [13–15], while pulmonary function test ILD indicated that 40–75% of cases presented with such a condition [13]. ILD occurs more often in the dcSSc phenotype than in the lcSSc (42% vs. 22%, $p < 0.001$) [10].

The predicting factors for ILD in SSc are considered to be the following [10]: age at the time of diagnosis of SSc, African American ethnicity, hypothyroidism, cardiac disease, elevated Rodnan score (i.e., a quantification scale of the affected cutaneous areas), forced vital capacity (FVC) less than 65% pred with a hazard ratio (HR) of 3.18 ($P < 0.001$), and carbon monoxide diffusion capacity (DLco) less than or equal to 55% pred ($HR = 3.02$, $P < 0.001$). Other identified risk factors are elevated creatinine and phosphocreatine kinase [16,17], autoantibodies such as anti-topoisomerase ($HR = 1.76$, $P = 0.002$) [18] and anti-endothelial cell antibodies [19] and the dcSSc ($P = 0.03$) [10,20].

The presence of pulmonary hypertension (PH) has been associated with older age at the time of diagnosis of SSc, gastroesophageal reflux (AOR 2.41, $p = 0.005$), dysphagia (AOR: 2.7, $P = 0.001$) [20], DLco less than 55% pred ($HR = 12.08$, $p < 0.001$) [10], high levels of serum

**Table 1**
Pulmonary involvement in scleroderma [adapted from 10].

| |
|---|
| Primary |
| *Pulmonary Parenchymal Disease* |
| Non-specific interstitial pneumonia |
| Usual interstitial pneumonia |
| Organizing pneumonia |
| Combined emphysema and pulmonary fibrosis |
| Diffuse alveolar damage |
| *Vascular Disease* |
| Pulmonary arterial hypertension |
| Occlusive venous pulmonary disease |
| Capillary Hemangiomatosis |
| Diffuse alveolar haemorrhage |
| Secondary |
| *Airway Disease due to Aspiration* |
| Aspiration bronchiolitis |
| Aspiration pneumonia |
| Lipoid pneumonia |
| Bronchiolocentric fibrosis |
| *Neoplasia* |
| *Infection* |
| *Diaphragmatic Weakness* |
| *Pulmonary Disease Secondary to Heart Disease* |
| *Medication Toxicity* |

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