

# Pleuroparenchymal fibroelastosis in patients affected by systemic sclerosis

## What should the rheumatologist do?

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### Abstract

Pleuroparenchymal fibroelastosis (PPFE) is a rare new interstitial lung disease (ILD) characterized by the fibrotic thickening of the visceral pleura and subadjacent parenchymal areas of the upper lobes. This study reveals that patients with ILD-SSc associated with chest HRCT evidence of PPFE require close and recurrent follow-up with periodic evaluation of lung function parameters, DLCO and chest HRCT. Rheumatologists should be aware of this new radiological finding which is accompanied by a negative prognosis, especially when associated with a progressive course. Patients with this radiological pattern need to be monitored with particular attention.

**Abbreviations:** DLCO = diffuse capacity for carbon monoxide, FEV<sub>1</sub> = forced expiratory volume in 1 second, FVC = forced vital capacity, HRCT = high resolution computed tomography, HP = hypersensitivity pneumonitis, ILD = interstitial lung diseases, LFT = lung function tests, NSIP = non-specific interstitial pneumonia, PPFE = pleuroparenchymal fibroelastosis, TLC = total lung capacity, UIP = usual interstitial pneumonia.

**Keywords:** interstitial lung diseases, pleuroparenchymal fibroelastosis, prognosis, systemic sclerosis

## 1. Introduction

Pleuroparenchymal fibroelastosis (PPFE) is a rare new interstitial lung disease (ILD) characterized by the fibrotic thickening of the visceral pleura and subadjacent parenchymal areas of the upper lobes.<sup>[1–3]</sup> Histological features of PPFE include aggregates of elastic fibers, especially in subpleural areas, and intra-alveolar collagenous fibrosis with septal elastosis (with or without collagen thickening of the visceral pleura).<sup>[3–5]</sup> First described 25 years ago,<sup>[6]</sup> PPFE is now

considered a distinct entity that may be familial, idiopathic, or associated with pathological conditions such as hypersensitivity pneumonitis (HP), pneumoconiosis, bone marrow or lung transplant, drug-induced lung toxicity, and connective tissue diseases.<sup>[6–12]</sup> PPFE may coexist with different radiological and histological ILD patterns: usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), granulomatous lung diseases, and chronic hypersensitivity pneumonitis (HP).<sup>[13]</sup> Radiological PPFE has also been reported in patients with recurrent respiratory infections, which is in line with the theory that repeated inflammatory stimuli may trigger the disease.<sup>[14]</sup> A high prevalence of PPFE-like lesions was recently detected by chest high resolution computed tomography (CT) in a cohort of patients with ILD related to connective tissue disorders.<sup>[15]</sup> This type of alteration was associated with a negative prognosis.<sup>[15]</sup>

Here we analyzed a cohort of 11 patients with PPFE associated with systemic sclerosis (SSc) in order to explore the clinical and radiological characteristics of this disease. Patients with PPFE associated with systemic sclerosis (2 men and 9 women, mean age 66.6 ± 15.8 years) were diagnosed according to international guidelines at Siena Referral Centre for ILD and Lung Transplant, Siena Rheumatology Unit and Careggi Referral Centre for Systemic Sclerosis. All patients had a radiological diagnosis of PPFE and a definite diagnosis of systemic sclerosis, as well as an observation period of almost 24 months. The clinical and functional details were analyzed retrospectively in relation to demographic data, smoking, occupational/environmental, and exposure history. The following parameters had been recorded: age, sex, bronchoalveolar lavage (BAL) differential cell count, lung function tests, and blood gas analysis parameters. Lung function test parameters had been measured according to ATS/ERS guidelines to obtain percentages of predicted forced expiratory

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The study was approved by Siena Local Ethics Committee C.E. A. V. S. E. (code number 180712).

The patients gave consent to participate under the "Ethics, consent, and permissions." The authors obtained consent to publish from the participants to report individual patient data.

No animals were involved. Informed consent is available for every patients.

All these authors have no potential conflicts of interest.

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**Table 1****The clinical and functional characteristics of patients with systemic sclerosis associated with pleuroparenchymal fibroelastosis.**

|                                    |                 |
|------------------------------------|-----------------|
| No. of patients                    | 11              |
| Male (%)                           | 2/11 (18)       |
| Age (mean $\pm$ SD)                | 66.6 $\pm$ 15.8 |
| Smoke (n=8): former:current:never  | 1:2:5           |
| Onset symptoms:                    |                 |
| • Dyspnoea                         | 6/8             |
| • Cough                            | 1/8             |
| • Pnx                              | 1/10            |
| • Crackles                         | 6/8             |
| • Clubbing                         | 3/6             |
| Pulmonary function tests onset     |                 |
| FEV <sub>1</sub> %                 | 80.6 $\pm$ 18   |
| FVC %                              | 80.1 $\pm$ 19.5 |
| DLCO %                             | 58.4 $\pm$ 30   |
| Pulmonary function tests follow up |                 |
| FEV <sub>1</sub> %                 | 59.5 $\pm$ 15.1 |
| FVC %                              | 60.9 $\pm$ 20.3 |
| DLCO %                             | 38.4 $\pm$ 18.7 |

DLCO = diffuse capacity for carbon monoxide, FEV<sub>1</sub> = forced expiratory volume in 1 second, FVC = forced vital capacity.

volume in 1 second (FEV<sub>1</sub>), forced vital capacity (FVC), and diffuse capacity for carbon monoxide (DLCO) values.<sup>[2]</sup> The study had been approved by the local ethics committee. Bronchoscopy with BAL collection had been performed in 9/11 patients for diagnostic purposes at the same time as blood gas analysis and lung function tests (LFT), after written informed consent. BAL samples had been obtained by instillation of 4 aliquots of 50 mL saline solution by fiberoptic bronchoscope. The aliquots had been immediately aspirated. The first BAL sample had been kept separate from the others and was not used for immunological tests. Sub-samples had been cultured for microbes, fungi, and viruses to exclude infections. Cells had been separated by centrifuge and the fluid fraction frozen for enzyme assays. Differential cell counts had been done. All

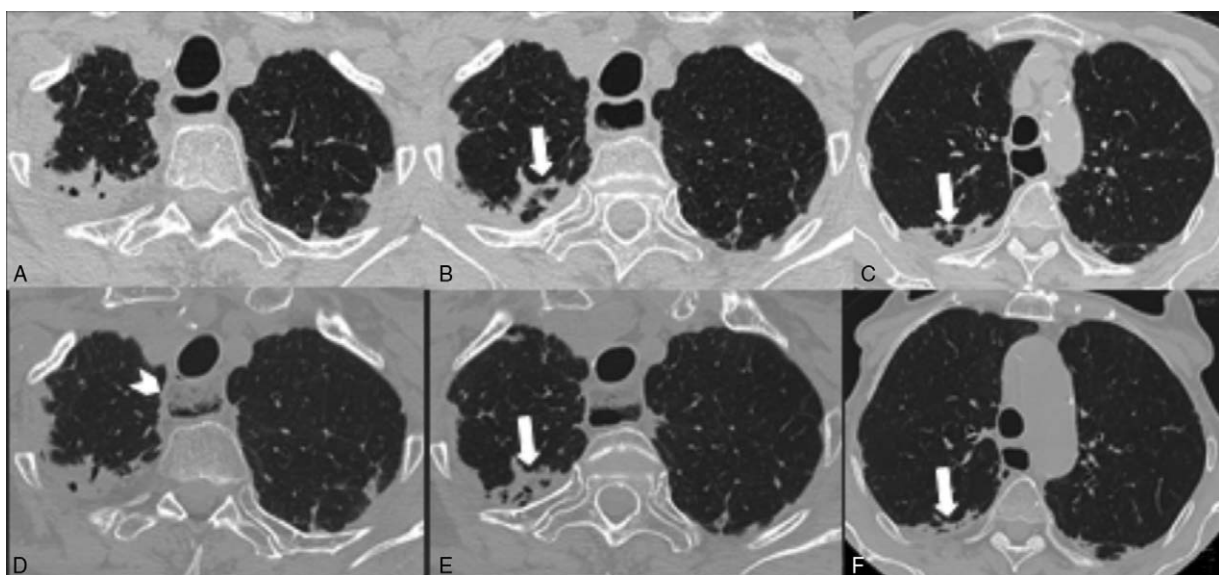
patients underwent chest x-ray in postero-anterior and lateral projections and chest high resolution CT of the chest (HRCT) at full inspiration at the time of ILD diagnosis. All CT scans were reviewed retrospectively by experienced radiologists for PPFE-like lesions (i.e., apical subpleural dense consolidations associated or not associated with pleural thickening). SSc patients with PPFE were identified on the basis of HRCT evidence of PPFE radiological features.

### 1.1. Demographic, clinical, and immunological features

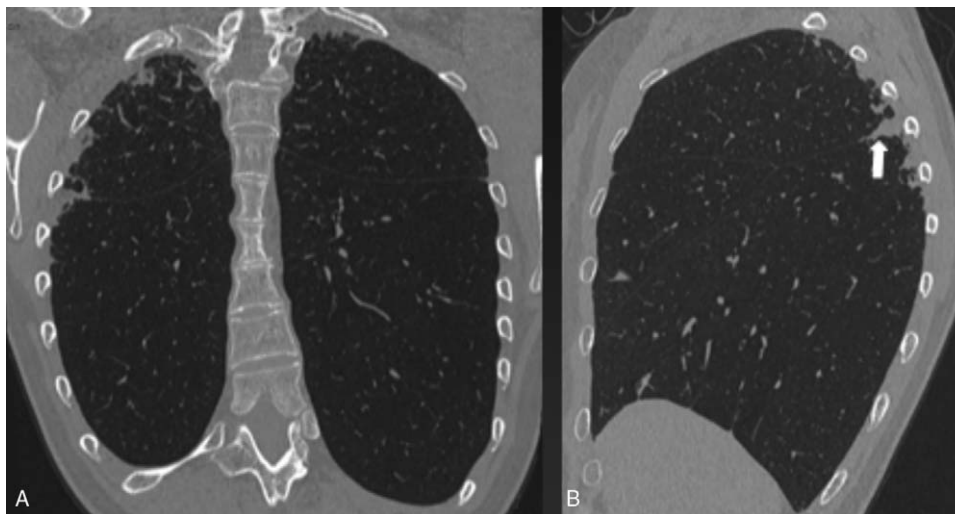
The clinical and demographic features of our population are summarized in Table 1. All patients were Caucasian and showed diffuse systemic sclerosis. The patients showed increased serum C-reactive protein levels (ranging from 6.9 to 1 mg/L); 6/11 patients showed speckled antinuclear antibody pattern with anti-Scl-70 positivity and 3/11 patients showed anti-U1-RNP antibodies. A single patient was asymptomatic at the first visit. The most common respiratory symptom was dyspnoea (Table 1); 1 patient showed spontaneous pneumothorax at onset and another developed pneumomediastinum 2 years after diagnosis. Most patients had bibasal crackles (Table 1). Blood gas analysis on room air revealed mild hypoxia (paO<sub>2</sub> 70.1  $\pm$  9.3 mmHg and paCO<sub>2</sub> 34.8  $\pm$  5.5 mmHg).

### 1.2. Radiological features

Chest HRCT revealed a radiological pattern of NSIP in 2 patients while the others a usual interstitial pneumonia (UIP) pattern, with lower-lobe-predominant peripheral and bibasal reticulations, traction bronchiectasis and honeycombing, and no ground-glass attenuations. The extent of emphysema in all patients was limited to a small percentage of parenchyma and was associated with smoking history. In all patients, PPFE radiological features showed upper-lobe-predominant focal pleural and subpleural thickenings and bilateral apical dense consolidations (Figs. 1 and 2). In a



**Figure 1.** (A–F) PPFE (A–C) in an 80-year-old woman with scleroderma involving the upper lobes and the apical segments of the inferior lobes including the fissures. Three years after the diagnosis (D–F) it is clear a mid increase of fibrosis, especially on the right side (arrows in B, C, E, F). The esophagus is dilated with food stagnation (arrowhead in D) due to the scleroderma involvement. PPFE = pleuroparenchymal fibroelastosis.

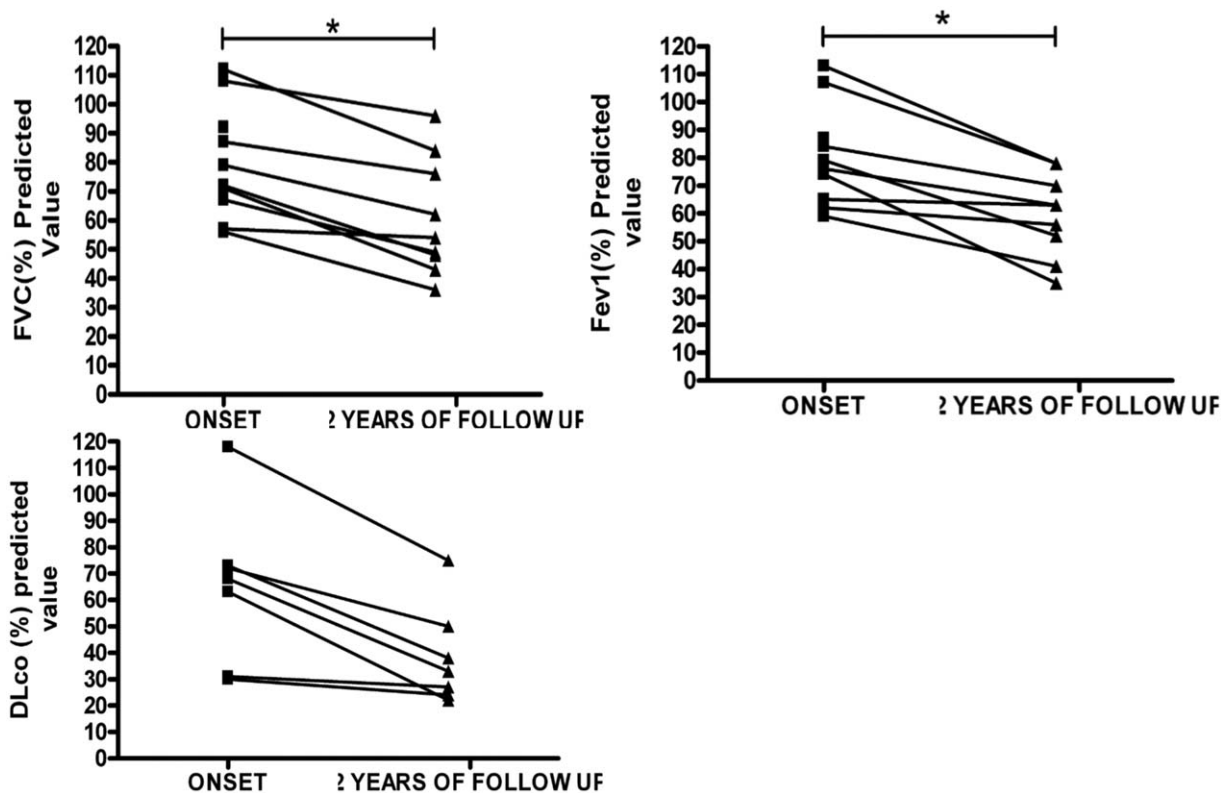


**Figure 2.** (A, B) PPFE in a 59-year-old woman with scleroderma and allergic asthma. Coronal-oblique (A) and sagittal (B) multiplanar reconstructions show the predominant involvement of the upper lobe and apical segment of the lower lobe on the right side. Note the involvement of the major fissure (arrow in B) that is atypical finding in PPFE. PPFE=pleuroparenchymal fibroelastosis.

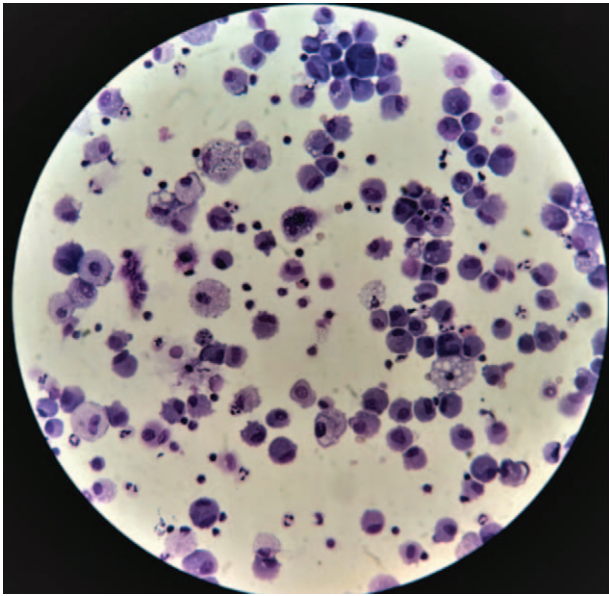
patient with advanced disease, the architectural distortion also involved adjacent and lower lobes (Fig. 2). At 12 to 18 months follow-up, chest HRCT was unchanged in 3/11 patients, 1 patient had undergone lung transplant due to rapid deterioration of the clinical condition and the others showed progressive worsening and evolution of radiological alterations with progressive involvement of the middle and lower lobes.

**1.3. Functional results**

Lung function parameters in this population were collected at onset of the disease and at 12 month follow-up: FEV<sub>1</sub> % was 80.6 ± 18 and FVC % 80.1 ± 19.5. DLCO % was depressed: 58.4 ± 30. At 2-year follow-up, patients had restrictive functional deficit and decreased diffusion capacity for carbon monoxide (DLCO) (Fig. 3A–C).



**Figure 3.** FVC (%), FEV<sub>1</sub> (%), and DLCO (%) predicted values in patients at the time of diagnosis and after 2 years of follow-up (\**P* < .05). DLCO=diffuse capacity for carbon monoxide, FEV<sub>1</sub>=forced expiratory volume in 1 second, FVC=forced vital capacity.



**Figure 4.** Bronchoalveolar lavage cellular populations from a patient affected by PPFE and systemic sclerosis. PPFE=pleuroparenchymal fibroelastosis.

#### 1.4. Bronchoalveolar lavage findings

BAL features revealed elevated BAL neutrophil and eosinophil percentages due to inflammatory interstitial lung involvement. BAL cell percentages were: macrophages  $73.4 \pm 50.2$ , lymphocytes  $20.1 \pm 17.8$ , neutrophils  $4.4 \pm 2.9$ , and eosinophils  $3.8 \pm 3$ . Figure 4 shows BAL cell populations, slight increase in polymorphonuclear cells and inflammatory foamy macrophages (about 5%). Figure 4 reports BAL cellular populations in a patient with PPFE associated with systemic sclerosis.

In conclusion, this retrospective study indicates the clinical importance of radiological evidence of PPFE in a cohort of patients with ILD-SSc. Radiological PPFE-like lesions were associated with increased risk of pneumothorax and pneumomediastinum, rapid lung function decline and poor prognosis. Most radiological alterations involved the upper lobes and were readily detected.

This is an important clinical finding worthy of further investigation: patients with ILD-SSc associated with chest HRCT evidence of PPFE require close and recurrent follow-up with periodic evaluation of lung function parameters, DLCO and chest HRCT. Rheumatologists should be aware of this new radiological finding which is accompanied by a negative prognosis, especially when associated with a progressive course. Patients with this radiological pattern need to be monitored with particular attention.

#### Author contributions

Contributions: Elena Bargagli proposed and developed the manuscript, Maria Antonietta Mazzei and Francesco Gentili developed the design of the study and analyzed HRCT of the chest, Orlandi Martina, Dott Paolo Cameli, Dott Francesca

Bellisai, Bruno Frediani, and Laura Bergantini performed the clinical evaluation, developed immunological analysis, statistical analysis and data collection, Loredana Carobene, Silvia Bellando Randone, Serena Guiducci and Bruni Cosimo collected clinical and functional data and Matucci Cerinic Marco developed the design of the study and manuscript preparation.

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