Combined pulmonary fibrosis and emphysema in systemic sclerosis: A syndrome associated with heavy morbidity and mortality

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ABSTRACT

Background. The syndrome of combined pulmonary fibrosis and emphysema (CPFE) primarily due to tobacco smoking has been reported in connective tissue disease, but little is known about its characteristics in systemic sclerosis (SSc).

Methods. In this retrospective multi-center case-control study, we identified 36 SSc patients with CPFE, and compared them with 72 SSc controls with interstitial lung disease (ILD) without emphysema.

Results. Rate of CPFE in SSc patients with CT scan was 3.6%, and 7.6% among SSc patients with ILD. CPFE-SSc patients were more likely to be male (75% *vs* 18%, $p<0.0001$), smokers (83% *vs* 33%, $p<0.0001$), and to have limited cutaneous SSc (53% *vs* 24% $p<0.01$) than ILD-SSc controls. No specific autoantibody was significantly associated with CPFE. At diagnosis, CPFE-SSc patients had a greater decrease in carbon monoxide diffusing capacity (DLCO 39±13% *vs* 51±12% of predicted value, $p<0.0001$) when compared to SSc-ILD controls, whereas lung volumes (total lung capacity and forced vital capacity) were similar. During follow-up, CPFE-SSc patients more frequently developed precapillary pulmonary hypertension (PH) (44% *vs* 11%, $p<10^{-4}$), experienced more frequent unscheduled hospitalizations (50% *vs* 25%, $p<0.01$), and had decreased survival ($p<0.02$ by Kaplan-Meier survival analysis) as compared to ILD-SSc controls.

Conclusions. The CPFE syndrome is a distinct pulmonary manifestation in SSc, with higher morbidity and mortality. Early diagnosis of CPFE by chest CT in SSc patients (especially smokers) may result in earlier smoking cessation, screening for PH, and appropriate management.

INTRODUCTION

Systemic sclerosis (SSc) is a rare multisystemic disease characterized by vascular hyper-reactivity and fibrosis in the skin and other organs. Fifty to 70% of SSc patients develop interstitial lung disease (ILD) (1) which represents one of the two main causes of death in SSc (2). In this setting, we recently reported 36 patients, including 10 with SSc, with CTD-associated combined pulmonary fibrosis and emphysema (CPFE) (3), a recently described entity of severe prognosis (4).

CPFE is defined by the association of centrilobular and/or paraseptal emphysema in upper lung zones and pulmonary fibrosis in lower lobes (4-11). In addition to connective tissue disease (CTD)-associated ILD (3, 12, 13), a number of etiologies have been reported to contribute to the CPFE syndrome including tobacco smoking, pneumoconiosis like asbestosis (6) or siderosis (14) and familial pulmonary fibrosis (15-17). Because of the opposing effects of emphysema and fibrosis on lung mechanics, the lung function profile is characterized by subnormal dynamic and static lung volumes despite significant reduction in carbon monoxide diffusing capacity (DLCO) and severe exercise hypoxemia. Approximately 30% of patients with idiopathic ILD also have significant emphysema and therefore present with CPFE. Most patients with CPFE are male smokers or ex-smokers. Pulmonary hypertension (PH), often severe, occurs in nearly 50% of CPFE patients, and seems tightly linked to increased mortality (4, 8, 18).

SSc-associated CPFE may exhibit unique characteristics that might not apply to other CTDs. Thus, in our study performed in CTD-associated CPFE, 5 out of 10 patients with SSc-associated CPFE, but none of the others, developed PH (3). Furthermore, increased susceptibility to emphysema has been suggested in SSc patients (15, 19).

In order to describe the specificities of SSc-associated CPFE (CPFE-SSc), we conducted a retrospective multi-center case-control study, and compared the clinical characteristics,

pulmonary function tests (PFTs), and outcome of 36 patients with CPFE-SSc with those of 72 control patients with SSc and ILD without emphysema (ILD-SSc).

PATIENTS AND METHODS

Selection of cases and controls

Physicians belonging to the National reference and the Regional competence centers for rare pulmonary diseases, to the Groupe d'Etudes et de Recherche sur les Maladies « Orphelines » pulmonaires (GERM « O »P), the Club Rhumatismes et Inflammation (CRI), and the Groupe Francophone de Recherche sur la Sclérodermie (GFRS), were asked to report all cases of CPFE occurring in a patient with SSc. The databases from the Centre de Référence Maladies Systémiques Autoimmunes Rares d'Ile de France (Cochin Hospital) and from the GERM « O »P were also screened for potential cases included between 1998 and June 2013. In order to estimate the prevalence of CPFE in SSc, all thoracic high resolution computed tomography (HRCT) scans of patients from the Cochin cohort readily available on digital support (from 2006 on) were reviewed (n= 276 patients).

Inclusion criteria were the following:

1) evidence of emphysema on HRCT scan, defined as areas of decreased attenuation, without visible walls, of non-uniform distribution and predominantly located in upper lung zones (20);

2) evidence of ILD, characterized by presence of ground glass opacities, reticulations, traction bronchiectasis or bronchiolectasis, and/or honeycombing;

3) SSc defined by the 2013 ACR-EULAR classification criteria (21);

4) Patients with ILD related to another etiology and patients with a diagnosis of mixed connective tissue disease were excluded.

For each CPFE-SSc patient, two control SSc patients corresponding to criteria 2, 3 and 4 but without emphysema were randomly selected from the Cochin database that included 773 patients at the end of the study period. This database collects socio-demographic, clinical, morphological, biological, and PFT characteristics of patients with SSc referred to this tertiary care center.

Details about data collection and thoracic HRCT scan analysis are described in the supplementary appendix.

Ethical considerations

Our study was approved by the Hotel Dieu Ethics Committee (Paris, France), the CCTIRS and the CNIL (French National Committee for Informatics and Liberties).

Statistical analysis

Statistical analysis was performed using XLSTAT 2013 software. Comparisons between discrete variables were made using Chi^2 or Fisher Exact Test. For continuous variables, comparisons were performed using an unpaired 2-tailed Student t-test or a Mann Whitney U test as appropriate. Survival analysis was performed with the Kaplan-Meier method using a Log Rank test. The effect of tobacco on survival was examined using a cox-model regression analysis Patients were censored if they were lost to follow-up. P values less than 0.05 were considered significant.

RESULTS

Patient population

Thirty-six patients with CPFE-SSc were identified, including 10 who had been previously reported (3, 15). Representative examples of HRCT scans from patients with CPFE-SSc are shown in Figure 1.

Out of 276 SSc patients from the Cochin cohort with HRCT scans readily available for review, ILD was detected in 131 patients (47.4%), of whom 10 also had significant emphysema. Thus, the rate of CPFE for all SSc patients evaluated on CT was 3.6%, and 7.6% among SSc patients with ILD. Although the difference did not reach statistical significance, emphysema seemed to be more frequent in SSc-ILD patients compared to SSc patients with no ILD (7.6% versus (*vs*) 2.7%, respectively, p=0.06), despite a similar proportion of smokers (35.5% and 40.0%, respectively).

Demographic characteristics and exposure to smoking and to aerocontaminants (Table 1)

Median age at the diagnosis of SSc was similar in ILD-SSc controls and CPFE patients. However, CPFE-SSc patients were more likely than ILD-SSc to be males (75% *vs* 18%, p<0.0001), smokers or former smokers (83% *vs* 33%, p<0.0001), and to report occupational exposure to dusts (35% *vs* 5%, p<0.0001). Among smokers, tobacco consumption was more important in CPFE patients (mean 31.7±20.2 pack-years) as compared to ILD-SSc controls (mean 19.3±12.6 pack-years, p=0.02). Interestingly, when analysis was restricted to smokers from each group, male gender remained strikingly more prevalent in CPFE-SSc patients (83% *vs* 25%, p<0.0001). Unadjusted OR for male gender was 13.6 (95% confidence interval: 5.2-35.7), or 9.5 (3.4-26.2) after adjustment for smoking status.

SSc clinical and immunological characteristics (Table 1)

The SSc subtype differed between CPFE-SSc and ILD-SSc patients ($p<0.01$). Namely, most CPFE-SSc patients exhibited a limited cutaneous form of SSc (53% *vs* 24% of ILD-SSc controls). Accordingly, the mean modified Rodnan skin score was higher in ILD-SSc controls. The proportion of patients with extra-pulmonary complications and autoantibody specificity did not differ between groups.

Lung disease clinical characteristics and symptoms (Table 1)

The delay between SSc diagnosis and the radiological evidence of CPFE was 3.2±5.4 years. In most cases (n= 24), emphysema and ILD were diagnosed simultaneously whereas ILD preceded emphysema in 9 patients by 3.6±3.5 years on average. In the remaining 3 patients, emphysema was detected before ILD. In the control group, ILD was identified 3.1±5.9 years after the diagnosis of SSc.

At the time of diagnosis, most patients reported dyspnea on exertion (97% and 86% of CPFE and ILD-SSc controls, respectively), but with increased dyspnea in CPFE-SSc as compared to ILD-SSc patients ($p<0.05$, Chi^2 for NYHA functional classes).

Pulmonary function tests (PFT) (Table 2)

At diagnosis, a restrictive ventilatory defect was observed in 21/36 CPFE patients (58%) and 37/72 ILD-SSc controls (53%, $p=0.6$). Forced vital capacity (FVC) and total lung capacity (TLC) were similar between groups (Table 2). CPFE-SSc patients exhibited a more severe decrease in DLCO (39±13 *vs* 51±12%, $p<0.0001$) and transfer coefficient of the lung (KCO 60±17% *vs* 74±15%, $p<0.0001$) than ILD-SSc controls. The composite physiologic index (CPI), calculated as described by Wells *et al.* (22), was significantly higher in the CPFE group.

Forty-eight percent of CPFE patients and 23% of ILD-SSc controls had hypoxemia at rest (PaO_2< 80 mmHg, p=0.01). At the end of the 6-minute walk test, 73% of CPFE patients, and 41% of ILD-SSc controls (p=0.01) exhibited a decrease in percutaneous saturation greater than 4%.

Upon follow-up, the presence of emphysema was surprisingly associated with a greater decline rate of FVC and TLC values, whereas the decline rate of DLCO was similar in both groups. Indeed, FVC decreased by a mean of 3.1±4.8% per year in CPFE patients, *vs* 1.1±4.5% per year in ILD-SSc controls (p<0.05). The mean interval from the diagnosis of CPFE or ILD to the last PFT available was comparable in both groups (4.8±3.3 years *vs* 5.7±4.0 years in CPFE and ILD-SSc controls, respectively).

Thoracic HRCT scans (Table 3)

Twenty-eight of the 32 patients analysed (88%) and 94% of ILD-SSc controls had CT features typical for non-specific interstitial pneumonia. CPFE patients had a significantly lower mean disease extent (28% (range: 5-55%) *vs* 19% (2-71%), p<0.01) although the mean traction bronchiectasis score was similar in both groups. Emphysema was predominantly paraseptal in 20 (62%) patients. Mean emphysema extent was 15% (range: 2-50%) with only 7 patients with emphysema extent of more than 20%. The CPFE pattern (as defined in (23)) was that of “distinct entities” in 10 patients, “progressive transition” between emphysema and fibrosis in 7 patients, “predominantly paraseptal” emphysema associated with fibrosis in 6 patients, and unclassifiable in the remaining 9 patients. Interestingly, the proportion of patients with main pulmonary artery diameter enlargement above 34 mm was significantly higher in CPFE patients than in the control group (22 (7%) *vs* 4 (3%), p=0.01).

Pulmonary hypertension (Table 4)

Systolic pulmonary arterial pressure (sPAP) could be estimated by echocardiography in 34 CPFE-SSc patients and in 67 ILD-SSc controls. Elevated sPAP> 40 mmHg or right heart cavities dilation was detected in 55% and 25% of CPFE-SSc patients, respectively (*vs* 20% and 3% of ILD-SSc controls, p<0.001 in both cases). The mean estimated sPAP was significantly higher in the CPFE-SSc group (43±13 mmHg *vs* 36±13 mmHg, p <0.01). Precapillary pulmonary hypertension (PH) was confirmed by right heart catheterization in 16 (44%) SSc patients and 8 (11%) ILD-SSc controls (p<0.0001). The mean survival time without PH from the onset of SSc was 15.4±2.1 years in CPFE *vs* 24.2±1.4 years in ILD-SSc controls, (p<0.0001 Log Rank test, Figure 2a). Among CPFE-SSc patients, those who developed PH had significantly decreased PaO2 at rest, greater desaturation during the six-minute walk test, and lower DLCO at the time of diagnosis of CPFE as compared to patients without PH (not shown).

Treatment

Approximately half of the patients in both groups (53% of CPFE-SSc and 49% of ILD-SSc controls) received intravenous cyclophosphamide (6 to 12 infusions of 0.7 g/m² each) in association with low dose glucocorticoids (10-15 mg per day) followed by oral mycophenolate mofetil or azathioprine as a maintenance therapy. One additional patient with CPFE received oral cyclophosphamide for 6 months. At the end of cyclophosphamide treatment, FVC improved (by more than 10%) in 13% of CPFE-SSc patients, was stable in 47 %, and worsened (by more than 10%) in 40%. Comparable results were obtained in ILD-SSc controls (FVC improved in 22%, remained stable in 56%, and worsened in 22% of cases, p=0.51)

Prognosis

The mean follow-up after the first SSc symptom was 10.1±6.4 and 11.2±7.3 years in CPFE-SSc and control patients, respectively. During follow-up, 50% of CPFE-SSc patients and 25% of ILD-SSc controls required at least one emergency hospitalization for cardio-respiratory failure ($p<0.01$). Causes for emergency hospitalization in CPFE patients were right heart failure (n=13), infectious pneumonia (n=11, including 1 case of *Pneumocystis jiroveci* pneumonia), exacerbation of ILD (n=5), pneumothorax (n=4), hemoptysis (n=2) and pulmonary embolism (n=2).

Twenty (56%) CPFE-SSc patients and 13 (18%) ILD-SSc controls ($p<0.0001$) received long term nasal oxygen therapy. One patient in each group was diagnosed with lung cancer. Two CPFE-SSc patients underwent pulmonary transplantation.

Thirteen patients (36% of CPFE-SSc patients and 18% of ILD-SSc controls, $p=0.04$) died in each group. The mean survival time from the first manifestation of SSc was 13.0±1.0 and 27.6±3.9 years in CPFE-SSc and control patients, respectively ($p<0.01$, LogRank Test, Figure 2b). Similar results were obtained when the survival time was estimated from the date of ILD/CPFE diagnosis (not shown) or after adjustment for CPI to take into account the confounding effect of fibrosis extension (not shown). In CPFE-SSc patients, in univariate analysis, the existence of PH was the only parameter significantly associated with mortality ($p=0.05$; LogRank test, Figure 2c), whereas gender, scleroderma subtype and auto-antibody specificity were not (not shown). Using the Cox model, in univariate analysis: the CPFE and smoking status are both associated with survival ($p = 0.013$ for CFPE, $p = 0.03$ for active or weaned smoking). However, neither of them remains significant on multivariate analysis ($p = 0.13$ for CFPE, $p = 0.29$ for tobacco).

DISCUSSION

We present a large case series of patients with SSc-associated CPFE. We confirmed the pulmonary function hallmark of the CPFE syndrome, with markedly reduced DLCO, disproportionate to the preserved lung volumes and mild or absent airflow obstruction. The prevalence of precapillary PH (44%) was comparable to that observed in "idiopathic" CPFE, but much greater than the 8-20% prevalence observed in SSc with or without ILD (13, 24, 25). Recently, in a cohort of SSc patients with ILD, Antoniou *et al.* (13) reported an even greater prevalence of the CPFE syndrome (12.5%) but a somewhat lower prevalence of PH in CPFE-SSc patients (24%). The difference between our two studies might be explained by a difference in the definition of significant emphysema (in their report, mean emphysema extent represented 5.5% of lung surface *vs* 15% in the present study). At last, we could demonstrate that patients with CPFE-SSc had a decreased survival as compared to ILD-SSc controls. Altogether, our findings establish CPFE in patients with SSc as a serious distinct condition with increased morbidity and mortality when compared to ILD-SSc without emphysema.

As reported in patients with CPFE without CTD (4), male gender and tobacco smoking were the main risk factors associated with CPFE in SSc patients, and OR for male gender after adjustment for smoking status was 9.5. Moreover, using the Cox model, in univariate analysis: the CPFE and smoking status were both associated with survival. However, neither of them remained significant on multivariate analysis, probably because these two variables are not independent.

In addition, although none of the patients met the criteria for the diagnosis of pneumoconiosis, we observed a significant association with CPFE syndrome and exposure to dusts. This finding is consistent with previous reports suggesting a role for agrochemical compounds (26), iron dusts (4, 14), or talc (27) in the pathogenesis of CPFE.

The pathophysiology of CPFE outside the setting of CTD is poorly understood (28). In SSc-associated CPFE, emphysema might be related to inflammatory processes dependent on the CTD itself. Our observation that CPFE was more frequently associated with limited

cutaneous SSc highlights the importance of pathological processes specific to the underlying CTD. Moreover, the average tobacco consumption was lower in SSc-associated CPFE than that reported in idiopathic CPFE (31 pack-years *vs* 40-70 pack-years in idiopathic CPFE). Six patients (17%) denied any exposure to tobacco smoke. We also found a trend for a greater frequency of emphysema in patients with ILD-SSc (7.6%), compared to patients with SSc without evidence of ILD on CT scan (2.7%). Our data are in agreement with the findings of Antoniou *et al*., who found a high prevalence of emphysema in ILD-SSc patients, even in never smokers (13, 19). The reasons for this apparent increased susceptibility to develop emphysema are unclear. Interestingly, a relative α1-antitrypsin deficiency, or an excess of neutrophil elastase levels in the serum of SSc patients were reported (29, 30). In Tsk-1 mice, a murine model of SSc with a duplication of the *fibrillin 1* gene and anti-topoisomerase-1 antibodies, lung emphysema develops spontaneously (31). We could not demonstrate a specific link between anti-topoisomerase-1 detection and CPFE in our patients, but auto-antibodies with other specificities might play a role. Indeed, high levels of anti-elastin autoantibodies have been described in patients with SSc (32), or tobacco induced emphysema (33), but not in idiopathic CPFE (34). Interestingly, increased susceptibility to tobacco induced emphysema was also reported in patients with rheumatoid arthritis and ILD (12).

The functional profile of CPFE-SSc patients was similar to that usually reported in "idiopathic" CPFE, with subnormal mean FVC and TLC values and little evidence of airway obstruction despite the existence of radiologic emphysema. In contrast, DLCO and KCO values were markedly reduced and significantly lower than in ILD-SSc control patients despite similar lung volumes. However, the lack of significant difference between the two groups for TLC and FVC values and the lower predicted RV values in patients with CPFE are unexpected. Due to the absence of emphysema (and subsequent air-trapping mechanism), we expected higher FVC and lower RV values in the group of ILD-SSc controls. This finding

may reflect a more advanced fibrosing disease mitigating the expected gas-trapping effect of emphysema in CPFE patients. Such hypothesis could be the consequence of a delay in the diagnosis of lung fibrosis in these patients. Emphysema distant from the ILD may not have an effect on FVC, as opposed to emphysema admixed to the fibrotic process (35), which was not analyzed in the present study. Alternatively, patients with CPFE might be affected by a more rapidly progressive disease. Thus, the rate of FVC and TLC decline was greater in CPFE patients than in ILD-SSc controls, contrasting with other studies in "idiopathic" CPFE which demonstrated a slower decline in lung volumes as compared to patients with idiopathic ILD (5) especially in individuals with emphysema extent greater than 15% at HRCT (36).

Identifying CPFE in SSc patients with ILD is highly relevant. CPFE was associated with increased mortality. Compared to ILD-SSc controls, CPFE-SSc patients appeared more symptomatic, with increased dyspnea, more frequent hypoxemia at rest, and more frequent desaturation upon exercise. During follow-up, CPFE patients more frequently required emergency hospitalization for cardio-pulmonary reasons, and long-term nasal oxygen therapy. The cumulative frequency rate of precapillary PH (44%) was four times greater than in patients with isolated ILD-SSc. Importantly, the presence of PH in CPFE patients was associated with decreased exercise capacity, and decreased survival, as reported outside the setting of CTD (4, 8).

Our study has several limitations, including its retrospective design. Patients from the control group were randomly selected from a large cohort of SSc patients emanating from a single center, whereas CPFE patients were identified in several university hospitals. This allowed random selection of ILD-SSc controls among a very large group of SSc patients to constitute a representative sample of the condition of interest and avoid important selection bias associated with the non-random selection of ILD-SSc controls in smaller centers.

In conclusion, CPFE is a distinct, still under-recognised, pulmonary complication of SSc. Patients with SSc-associated CPFE more frequently develop PH and show increased morbidity and mortality as compared to those with SSc and ILD without emphysema.

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LEGEND TO FIGURES

Figure 1:

(A) Paraseptal emphysema with bullae in the upper lung zones, with right upper lobe predominance. (B) Mid-lung CT image demonstrates associated ground glass opacities and intralobular reticulations, consistent with fibrotic changes. The hypoattenuating areas in the lingula correspond to a combination of paraseptal emphysema and honeycombing. (C) Centrilobular areas of decreased attenuation without visible walls, typical for centrilobular emphysema, predominantly in the right upper lobe. (D) Lower lung zones showing ground glass opacities with fine intralobular reticulations and traction bronchiectasis, consistent with fibrosis, nonspecific interstitial pneumonia pattern.

Figure 2: a) Occurrence of precapillary pulmonary hypertension (PH) in CPFE-SSc and ILD-SSc patients (Kaplan-Meier analysis, $p<0.0001$. LogRank test). Precapillary PH was diagnosed based on right heart catheterization findings. **b)** Survival of CPFE-SSc and ILD-SSc patients (Kaplan-Meier analysis, $p<0.01$. LogRank test). **c)** Survival of CPFE patients according to the existence of precapillary PH (Kaplan-Meier analysis, $p=0.05$. LogRank test). Survival time (in years) for figure 2a, 2b, 2c is calculated from the date of the first SSc symptom excluding Raynaud phenomenon. Dots represent patients lost to follow-up. The remaining number of patients at risk is indicated below the timeline.

FIGURES

Figure 1

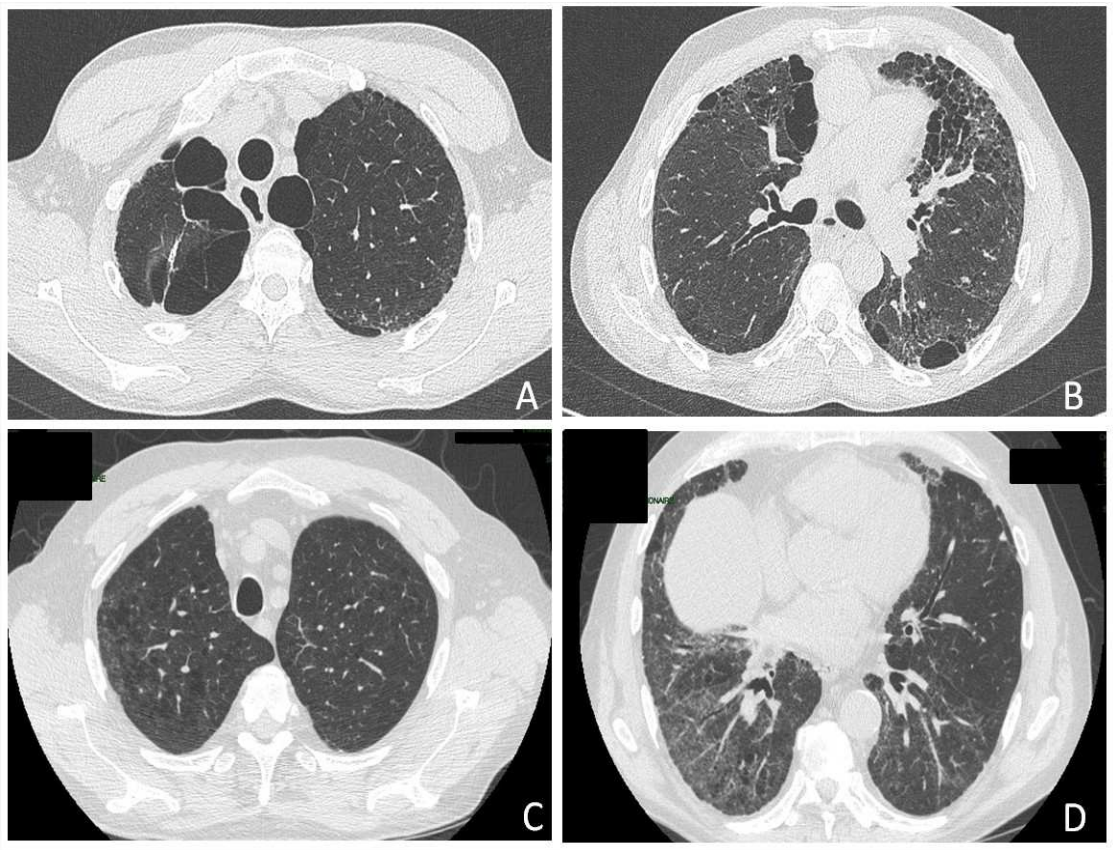

Figure 2

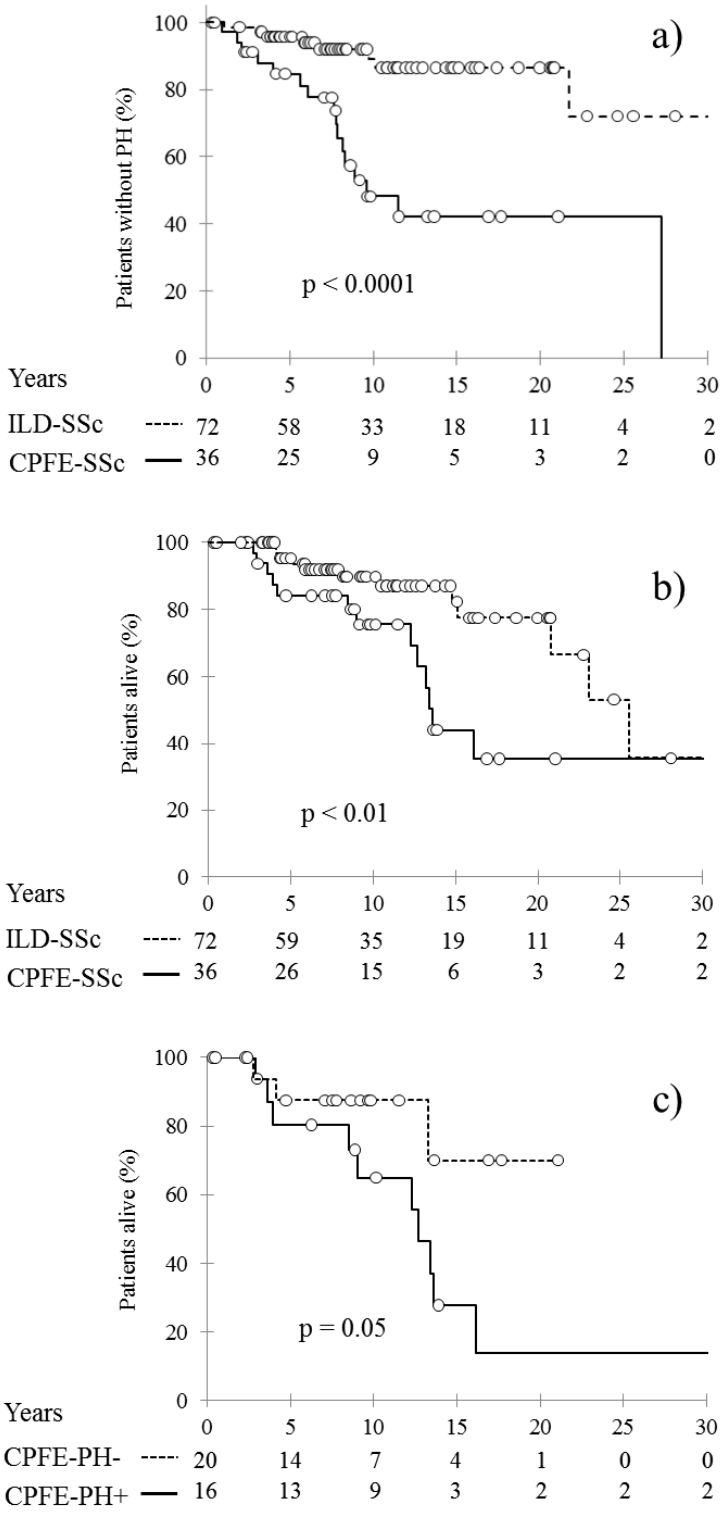
a)
Patients without PH (%)
100
80
60
40
20
0
p < 0.0001
Years
0 5 10 15 20 25 30
ILD-SSc 72 58 33 18 11 4 2
CPFE-SSc 36 25 9 5 3 2 0
b)
Patients alive (%)
p < 0.01
Years
0 5 10 15 20 25 30
ILD-SSc 72 59 35 19 11 4 2
CPFE-SSc 36 26 15 6 3 2 2
c)
Patients alive (%)
p = 0.05
Years
0 5 10 15 20 25 30
CPFE-PH- 20 14 7 4 1 0 0
CPFE-PH+ 16 13 9 3 2 2 2

Table 1 Clinical and immunological characteristics in CPFE-SSc patients and ILD-SSc controls.

	CPFE-SSc (n=36)	**ILD-SSc (n=72)**	p
Demographic characteristics			
Age at SSc diagnosis (median, range)	53 (15-74)	50 (13-74)	0.49
Males	27 (75%)	13 (18%)	**$<10^{-4}$**
BMI (kg/m2) (mean ± SD)	24.7 ± 3.8	24.3 ± 3.9	0.63
Smoker or ex-smokers	30 (83%)	24 (33%)	**$<10^{-4}$**
Smokers : tobacco consumption (mean ± SD)	31.7 ± 20.2	19.3 ± 12.6	0.02
Dust exposure *	12 (35%)	3 (5%)	**$<10^{-4}$**
SSc clinical characteristics			
SSc subtype (L/LC/D)	3/19/14 (8/53/39%)	2/18/52 (3/25/72%)	**<0.01**
MRSS (mean ± SD)	13.1 ± 10.0	18.5 ±12.0	**<0.05**
Raynaud phenomenon	35 (97%)	71 (99%)	0.61
Digital ulcers	21 (58%)	50 (69%)	0.25
Myositis (biopsy proven)	2 (6%)	13 (18%)	0.14
Joint pain	19 (53%)	48 (67%)	0.16
Severe gastro-intestinal symptoms	4 (11%)	9 (13%)	0.81
Myocarditis	6 (17%)	17 (25%)	0.35
Renal Crisis	0	7 (10%)	0.09
Lung disease characteristics			
Years between SSc and CPFE diagnosis (mean ± SD)	3.2 ± 5.4	N/A	
Years between SSc and ILD diagnosis (mean ± SD)	2.5 ± 5.3	3.1 ± 5.9	0.64
Dyspnea	35 (97%)	62 (86%)	0.10
NYHA functional classes (I/II/III/IV)	1/19/13/3 (3/53/36/8%)	9/42/21/0 (13/58/29/0%)	**0.03**
Chronic cough	15 (42%)	16 (22%)	**0.03**
Crackles	22 (71%)	44 (72%)	0.84
Ronchi	2 (6%)	2 (3%)	0.60
Finger clubbing	4 (11%)	2 (3%)	0.18
Right heart failure signs	8 (22%)	7 (10%)	**0.08**
Lipothymia	2 (6%)	0	0.11
Autoantibodies			
ANA	35 (97%)	69 (97%)	0.99
Anti-centromere	0	1 (1%)	0.47
Anti-topoisomerase I	15 (42%)	41 (58%)	0.12
Anti-RNA polIII	0	2 (3%)	0.65
Anti-Pm/Scl	0	0	1.0
Anti-Fibrillarin	1 (3%)	0	1.0
Anti-SSA	1 (3%)	2 (3%)	1.0
Anti-RNP	1 (3%)	4 (6%)	0.66

*Dust exposure was inferred from our knowledge of patients' profession and included exposure to flour, metal, wood, and concrete dusts. SSc subtype corresponds to the Leroy and Medsger 2001 classification (L= limited, LC=limited cutaneous, D=Diffuse). ANA: antinuclear antibody. BMI: body mass index; CFPE: combined fibrosis and pulmonary emphysema; ILD: interstitial lung disease; MRSS: modified Rodnan Skin Score; NYHA: New York Heart Association; Pm/Scl: polymyositis/scleroderma. RNP: ribonucleoprotein. RNA: ribonucleic acid; SD: standard deviation; SSc: systemic sclerosis. Unless specified, data are presented as patient number (percentage)

Table 2 Pulmonary function tests at diagnosis and over follow-up in CPFE-SSc and ILD-SSc patients

	CPFE-SSc	**ILD-SSc**	p	Patients tested (n CPFE/n control)
Pulmonary function tests at diagnosis				
RV (% pred)	89 ± 34	92 ± 27	0.33	36/70
TLC (% pred)	78 ± 17	79 ± 15	0.42	36/71
FEV1 (% pred)	75 ± 21	79 ± 20	0.69	36/70
FVC (% pred)	78 ± 18	77 ± 20	0.93	36/71
FEV1/FVC (%)	80 ± 10	87 ± 4	**0.04**	36/70
DLCO (% pred)	39 ± 13	51 ± 12	< **0.0001**	36/64
KCO (% pred)	60 ± 17	74 ± 15	< **0.0001**	36/64
CPI	49.8 ± 11.8	43.8 ± 11.7	< **0.01**	36/64
PaO_2 at rest (mmHg)	79.7 ± 13.3	86.9 ± 10.5	**0.01**	32/56
6-min walk test at diagnosis				
Walking distance (m)	401 ± 130	457 ± 92	0.08	26/42
Walking distance (% pred)	66 ± 18	79 ± 24	**0.02**	26/42
End SpO_2(%)	86.6 ± 9.6	92.6 ± 4.0	< **0.01**	26/40
Decrease in SpO_2 (%)	-9.0 ± 9.5	-3.6 ± 4.3	< **0.01**	26/40
Pulmonary functional parameters evolution over follow-up				
ΔRV (% pred/year)	-3.9 ± 9.3	0.5 ± 8.3	0.11	32/50
ΔTLC (% pred/year)	-2.7 ± 3.5	-0.6 ± 3.2	< **0.01**	32/61
ΔFEV1 (% pred/year)	-1.9 ± 5.7	-1.0 ± 5.3	0.59	33/56
ΔFVC (% pred/year)	-3.1 ± 4.8	-1.1 ± 4.5	**0.05**	33/60
ΔFEV1/FVC (%/year)	0.5 ± 2.4	0.2 ± 2.0	0.79	33/56
ΔDLCO (% pred/year)	-2.3 ± 3.3	-1.8 ± 3.3	0.23	31/46
ΔKCO (% pred/year)	-1.7 ± 4.2	-1.1 ± 5.3	0.35	31/46
ΔCPI (/year)	2.4 ± 3.1	1.2 ± 2.6	**0.03**	31/46
ΔPaO2 at rest (mmHg/year)	-4.0 ± 5.7	-1.3 ± 5.1	0.06	19/40

CPI, composite physiologic index; DLCO, Carbon monoxide diffusion capacity ; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; KCO, carbon monoxide transfer coefficient; PaO2: Oxygen arterial pressure. RV, residual volume; TLC, total lung capacity; % pred, percentage of predicted value. The Δ symbol indicates the variation of the parameter between the first and last measurements divided by the duration of follow-up in years. All values are presented as mean ± SD.

Table 3 High-resolution computed tomography findings in CPFE-SSc and ILD-SSc patients

	CPFE-SSc (n=32)	ILD-SSc (n=69)	p value
ILD pattern			0 .26
Non-specific interstitial pneumonia	28 (88)	65 (94)	
Other	4 (12)	4 (6)	
Zonal predominance of ILD			0.32
Upper lung zones or uniform	3 (9)	2 (3)	
Lower lung zones	29 (91)	67 (97)	
Anatomic distribution of ILD			0.10
Subpleural predominance	25 (78)	64 (93)	
Central predominance	2 (6)	1 (1)	
Uniform or diffuse	5 (16)	4 (6)	
ILD extent (%)	28 ± 14	19 ± 13	**<0.01**
[0-20%]	11 (34)	42 (61)	
]20-30%]	10 (32)	16 (23)	
]30-71%]	11 (34)	11 (16)	
Traction bronchiectasis score	5 ± 4	5 ± 4	0.85
[0-5]	17 (53)	48 (70)	
]5- 10]	12 (38)	17 (25)	
]10- 15]	3 (9)	4 (6)	
Emphysema pattern			
Paraseptal predominant	20 (62)	-	
Centrilobular predominant	12 (38)	-	
Bullae			
Present	8 (25)	-	
Absent	24 (75)	-	
Emphysema extent			
[0-5%]	10 (31)	-	
]5-10%]	11 (34)	-	
]10-20%]	4 (13)	-	
]20-50%]	7 (22)	-	
Relative extension of emphysema versus ILD			
ILD > emphysema	19 (60)	-	
ILD = emphysema	10 (31)	-	
ILD < emphysema	3 (9)	-	
Main pulmonary artery enlargement > 34 mm	7 (22)	3 (4)	0.01
Esophageal dilatation	14 (44)	28 (41)	0.83
CPFE pattern			
Distinct entities	10 (31)	-	-
Progressive transition	7 (22)	-	-
Paraseptal type	6 (19)	-	-
Unclassifiable	9 (28)	-	-

Radiological characteristics of interstitial lung disease (ILD) and emphysema of 32 CPFE-SSc and 69 ILD-SSc patients are reported. In the remaining 4 CPFE-SSc patients and 3 ILD-SSc, image quality was insufficient to allow detailed analysis. Details about calculation of disease extension, and traction bronchiectasis score are given in the supplementary appendix. The four categories of CPFE pattern are described in [23]

Table 4	Pulmonary hypertension evaluated by echocardiography and right heart catheterization in CPFE-SSc and ILD-SSc control patients.		
	Echocardiography		
	CPFE-SSc	ILD-SSc	
Subjects (n)	34	67	
Systolic PAP (mmHg, mean ± SD)	43 ± 13	36 ± 13	**< 0.01**
Systolic PAP > 40 mmHg (n, %)	18 (55%)	13 (20%)	**$< 10^{-3}$**
Right heart cavities dilation (n,%)	9 (25%)	2 (3%)	**$< 10^{-3}$**
	Right heart catheterization		
	CPFE-SSc	ILD-SSc	
Precapillary PH (n, %)	n = 16 (44%)	n = 8 (11%)	**$< 10^{-4}$**
Mean PAP (mmHg)	38.5 ± 9.6	39.1 ± 10.7	0.93
Right atrial pressure (mmHg)	6.9 ± 5.2	11.0 ± 6.8	0.21
PAWP (mmHg)	8.9 ± 3.6	9.6 ± 4.7	0.85
CI (l/min/m^2)	2.9 ± 0.6	3.0 ± 0.7	0.57
PVR (dyn.s.cm-5)	469 ± 229	587 ± 313	0.30

Right heart catheterization was performed in 21 CPFE-SSc patients and 10 ILD-SSc controls. Hemodynamic parameters (means ± SD) are shown only for patients with confirmed precapillary pulmonary hypertension (PH). CI: cardiac index; PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance.