

Original Article

Idiopathic pulmonary fibrosis and emphysema in smokers*

Fibrose pulmonar idiopática simultânea a enfisema em pacientes tabagistas

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Abstract

Objective: To describe the clinical and functional findings recently reported in the medical literature for patients diagnosed with emphysema involving the upper lobes and idiopathic pulmonary fibrosis (IPF) involving the lower lobes. **Methods:** Eleven patients with emphysema and IPF were identified retrospectively. All of the patients underwent high-resolution computed tomography of the lung and pulmonary function tests. **Results:** Of the 11 patients, 8 were male and 3 were female. The mean age was 70.7 ± 7.2 years (range, 61-86 years). All of the patients were smokers (mean smoking history, 61.5 ± 43.5 pack-years). The mean values of forced vital capacity (FVC), forced expiratory volume in one second (FEV₁) and FEV₁/FVC were $72.1 \pm 12.7\%$, $68.2 \pm 11.9\%$ and 74.4 ± 10.8 , respectively. Lung volumes were normal in 7 patients. A restrictive pattern was observed in 3 patients, and hyperinflation was present in one. The diffusing capacity was moderately-to-severely reduced in all of the patients (mean, $27.7\% \pm 12.9\%$ of predicted). Ten of the 11 patients performed the six-minute walk test. The mean distance covered was 358.4 ± 143.1 m, and 9 of the 10 patients presented desaturation $\geq 4\%$. Echocardiographic findings suggestive of pulmonary hypertension were present in 4 patients (mean systolic pulmonary artery pressure, 61.8 mmHg; range, 36-84 mmHg). **Conclusions:** The concomitant presence of emphysema and IPF causes characteristic changes on pulmonary function tests. The most significant finding is a discrepancy between diffusing capacity and spirometry results.

Keywords: Pulmonary emphysema; Pulmonary fibrosis; Lung Diseases, interstitial; Anoxia; Hypertension, pulmonary.

Resumo

Objetivo: Descrever os achados clínicos e funcionais de pacientes com enfisema em lobos superiores e fibrose pulmonar idiopática (FPI) em lobos inferiores, recentemente descrita na literatura. **Métodos:** Um grupo de 11 pacientes com a presença simultânea de enfisema e FPI foi identificado retrospectivamente. Todos os pacientes realizaram tomografia computadorizada de tórax com alta resolução e provas de função pulmonar. **Resultados:** Entre os 11 pacientes identificados, havia 8 homens e 3 mulheres, com média de idade de $70,7 \pm 7,2$ anos (variação, 61-86 anos). Todos os pacientes eram tabagistas (carga tabágica, $61,5 \pm 43,5$ anos-maço). As médias da capacidade vital forçada (CVF), do volume expiratório forçado no primeiro segundo (VEF₁) e da relação VEF₁/CVF foram $72,1\% \pm 12,7\%$, $68,2\% \pm 11,9\%$ e $74,4 \pm 10,8$, respectivamente. Os volumes pulmonares foram normais em 7 pacientes. Um padrão restritivo foi observado em 3 pacientes e hiperinsuflação estava presente em um. A capacidade de difusão pulmonar apresentou redução moderada a grave em todos os pacientes (média, $27,7\% \pm 12,9\%$ do previsto). No teste da caminhada de seis minutos, realizado por 10 pacientes, a distância caminhada média foi de $358,4 \pm 143,1$ m, ocorrendo dessaturação $\geq 4\%$ em 9 pacientes. Achados ecocardiográficos sugestivos de hipertensão pulmonar estavam presentes em 4 pacientes (média da pressão sistólica da artéria pulmonar, 61,8 mmHg; variação, 36-84 mmHg). **Conclusões:** A presença simultânea de enfisema e FPI causa alterações características nas provas de função pulmonar. O achado mais importante é a discrepância entre a capacidade de difusão e a espirometria.

Descritores: Enfisema pulmonar; Fibrose pulmonar; Doenças pulmonares intersticiais; Anóxia; Hipertensão pulmonar.

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Introduction

Smoking is a major cause of morbidity and premature death. In Brazil, it is estimated that there are 200,000 smoking-related deaths annually.⁽¹⁾ Among the most common effects of smoking are chronic obstructive pulmonary disease (COPD) and bronchogenic carcinoma. In 1990, COPD was the sixth leading cause of death worldwide. However, it may become the third leading cause of death by 2020, despite public health interventions.⁽²⁾ In Latin America, COPD-related deaths increased approximately 65% in the last decade.⁽³⁾

Interstitial lung diseases, such as respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, and Langerhans-cell histiocytosis, have also been associated with smoking.^(4,5) The role of smoking in these diseases is suggested by the clinical and radiological improvement that can occur after smoking cessation, as well as by the presence of combinations of these diseases in the same patient. The co-existence of the three patterns in the same patient has been previously reported.^(5,6)

Smoking also seems to be a risk factor for the development of idiopathic pulmonary fibrosis (IPF). The prevalence of tobacco use in IPF ranges from 41% to 83%, depending on the case definition used in the studies.^(6,7) In one case-control study, smoking was identified as a potential risk factor for IPF (OR = 1.6).⁽⁸⁾

Some cases of emphysema in the upper lobes and pulmonary fibrosis in the lung bases were recently described. These patients present normal spirometry results or mild airway obstruction, and relatively preserved pulmonary volumes, however, with a severe reduction in the diffusing capacity of the lung for carbon monoxide (DLCO). In addition, severe hypoxemia and pulmonary hypertension (PH) may be found.⁽⁹⁾

In the present study, we describe the clinical and functional aspects of 11 patients with emphysema and IPF.

Methods

A retrospective case study was carried out involving patients with concomitant emphysema and IPF, treated in the pulmonology outpatient clinic of a university hospital. The study was approved by the ethics in research committee of the institution.

Patients having received a clinical and radiological diagnosis of concomitant emphysema and IPF were included in the study. The IPF diagnosis was based on the criteria established by the American Thoracic Society and the European Respiratory Society.⁽¹⁰⁾ The major criteria are as follows: the exclusion of other known causes of interstitial lung disease, such as drug toxicity, environmental exposure, and collagen-related diseases; abnormal pulmonary function, with evidence of restriction, that is, reduced vital capacity, often with higher forced expiratory volume in one second/forced vital capacity (FEV₁/FVC) ratios or decreased gas exchange—increased alveolar-arterial oxygen gradient, decreased arterial oxygen tension (PaO₂), at rest or after exercise, or decreased DLCO; reticular abnormalities in both lung bases with minimal areas of ground-glass opacity seen on high-resolution computed tomography (HRCT); and transbronchial biopsy (TBB) or bronchoalveolar lavage (BAL) with characteristics that do not suggest an alternative diagnosis. The minor criteria are age > 50 years, unexplained insidious onset of dyspnea on exertion, duration of disease > 3 months and inspiratory crackling rales in both lung bases. In immunocompetent adults, the presence of all major criteria, as well as at least three of the four minor criteria, allows the clinical and radiological diagnosis of IPF.

The tomographic diagnosis of emphysema was based on the following findings: well-delineated areas of low attenuation (in comparison with contiguous areas of normal lung), surrounded by a very thin wall (<1 mm) or without a wall, or multiple bullae (>1 cm) predominantly in the upper lobes.⁽¹¹⁾ The tomographic definition of IPF was based on the following criteria: diffuse parenchymatous pulmonary disease with significant pulmonary fibrosis, defined as reticular opacities predominant in the lung periphery or bases, honeycombing; architectural distortion/traction bronchiectasis or bronchiolectasis; ground-glass opacities or areas of alveolar consolidation might be seen in conjunction, but should not be prominent.⁽¹²⁾ The tomography scans of the chest were reviewed by two of the authors at the time of the evaluation for inclusion in the study. The descriptions of the tomographic findings were based on radiological charts.

The exclusion criteria used in this study were as follows: other idiopathic interstitial pneumonias; collagen-related diseases; immunodeficiencies;

drug-induced pulmonary disease; pneumoconioses; hypersensitivity pneumonia; sarcoidosis; pulmonary histiocytosis; lymphangiomatosis; and eosinophilic pneumonia.

All patients were submitted to pulmonary function tests (spirometry with bronchodilator, pulmonary volumes and capacities measured by plethysmography and DLCO) according to guidelines for pulmonary function tests from the Brazilian Thoracic Association.⁽¹³⁾ The reference values for the Brazilian population were used in this study.⁽¹⁴⁻¹⁶⁾

Data collected from medical charts included smoking history, comorbidities, body mass index, occupational/environmental exposure, symptoms of gastroesophageal reflux, drug use, home oxygen therapy, and degree of dyspnea measured using the Modified Medical Research Council Dyspnea Scale (MMRC).⁽¹⁷⁾ In addition, data from other complementary tests were collected. Such data included the results of six-minute walk tests, blood gas analyses, echocardiograms, right heart catheterizations, and bronchoscopic examinations. Data registered during the most recent medical appointment, as well as most recent additional examinations, were used in this study.

Data were inserted and analyzed in a database using the program Microsoft Excel XP®. A descriptive analysis of the variables under study was performed. Quantitative data are presented as mean \pm standard deviation. Qualitative data are expressed as absolute numbers and percentages.

Results

The principal characteristics of the patients are shown in Table 1. Of the 11 patients, 8 were male. The mean age was 70.7 ± 7.2 years (range, 61-86 years). All patients were smokers. The mean tobacco intake was 61.5 ± 43.5 pack-years (range, 25-174 pack-years). The mean body mass index was 26.5 ± 4.6 kg/m² (range, 22.0-38.7 kg/m²). In the final appointment, the mean dyspnea score (MMRC scale) was 1.7 ± 1.4 . Of the 11 patients, 8 presented digital clubbing and 1 used home oxygen therapy. All patients used bronchodilators regularly. Other drugs used were hydrochlorothiazide, furosemide, captopril (5 patients) and citalopram (1 patient). Gastroesophageal reflux was present in 1 patient who used omeprazole regularly.

The time between the onset of symptoms and diagnosis was 14.4 ± 14.9 months (range, 3 months to 3 years). The mean time since diagnosis was 3.0 ± 2.3 years. In 9 cases, the diagnosis of emphysema and fibrosis was concomitant. Of the other 2 cases, 1 was initially diagnosed with fibrosis, and 1 was initially diagnosed with emphysema.

According to reference equations for the Brazilian population, the mean FVC (predicted %), FEV₁ (predicted %) and FEV₁/FVC ratio were $72.1\% \pm 12.7\%$, $68.2\% \pm 11.9\%$ and 74.4 ± 10.8 , respectively. The pulmonary volumes were normal in 7 of the 11 patients; mild hyperinflation (total lung capacity, 124.3% of predicted) was detected in 1 patient. Pulmonary restriction was demonstrated in the remaining 3 patients, with total lung capacity ranging from 65.1% to 80.0% of predicted, and residual volume ranging from 83.7% to 131.7% of predicted. The DLCO (% predicted) showed a severe decrease in 8 cases and a moderate decrease in 3 patients, with a mean of $27.7 \pm 12.9\%$.

On chest X-rays and HRCT scans, all patients presented findings consistent with emphysema and IPF (Figures 1 and 2). Radiotransparent areas were seen in the upper lobes on X-rays in all cases. Reticular opacities were present in the lung bases in 6 cases. All but 2 patients presented honeycombing. Areas of attenuation appeared as ground-glass opacities in 4 cases. Traction bronchiectasis was described in 3 of the 11 cases. Of the total number of patients in this study, 5 presented a PaO₂ < 70 mmHg at rest, which was determined by arterial blood gas analysis on room air. The mean pH, arterial carbon dioxide tension, bicarbonate, PaO₂, and arterial oxygen saturation were 7.44 ± 0.03 , 32.8 ± 6.7 mmHg, 21.5 ± 3.6 mmol/L, 68.9 ± 11.9 mmHg, and $94.2\% \pm 3.3\%$, respectively. None of the patients presented hypercapnia.

The six-minute walk test was performed by 10 patients—1 patient did not perform the test due to difficulty in walking. The mean distance walked was 358.4 ± 143.1 m, and 9 patients presented desaturation $\geq 4\%$ during the test. The mean peripheral oxygen saturation was $94.8\% \pm 2.4\%$ before the test and $86.2\% \pm 6.6\%$ after the test. The mean initial heart rate was 83.9 ± 18.8 bpm, and the mean final heart rate was 110.6 ± 21.2 bpm. The initial respiratory rate was 24.5 ± 6.5 breaths/min, and the final respiratory rate was 35.2 ± 7.1 breaths/min.

Table 1 – Principal characteristics of the 11 patients diagnosed with emphysema in the upper lung lobes and with alterations consistent with idiopathic pulmonary fibrosis in the lower lobes.

Patient	Gender/Age (years)	Smoking (pack-years)	FVC, % (L)	FEV ₁ , % (L)	FEV ₁ /FVC	TLC, % (L)	RV, % (L)	DLCO, % (mL/min/ mmHg)	Distance covered on the 6MWT (m)	Desaturation during the 6MWT (%)	PaO ₂ at rest (mmHg)
1	M/61	40	68.4 (2.75)	70.2 (2.26)	82.1	80.6 (4.75)	102 (2.01)	17 (5.25)	-	-	48.0
2	M/64	45	84.7 (3.54)	89.4 (2.94)	83.1	87.9 (5.59)	89.9 (1.88)	49.2 (15.6)	513	0	94.4
3	F/69	43	49.7 (1.46)	44.8 (1.08)	74.0	80 (3.24)	131.7 (1.66)	20.7 (4.41)	108	9	57.3
4	M/72	100	78.4 (3.12)	72.9 (2.23)	71.4	83.3 (5.30)	76.9 (1.70)	26.7 (8.2)	462	13	74.2
5	F/75	54	73.1 (2.77)	55.4 (1.6)	57.8	119.1 (6.18)	171.8 (3.11)	38.1 (9.25)	395	7	71.2
6	M/70	37	78.3 (2.99)	81.8 (2.43)	81.3	81 (4.96)	85.9 (1.84)	9.2 (2.79)	351	15	68.1
7	M/75	112	60.4 (2.49)	62.1 (1.93)	77.5	75.5 (5.42)	121.8 (2.91)	40.9 (13.3)	307	4	70.9
8	M/74	174	57.9 (2.28)	70.1 (2.11)	92.5	65.1 (4.29)	83.7 (1.90)	16.7 (5.19)	248	11	71.7
9	M/86	25	75.9 (2.52)	65.9 (1.62)	64.3	109.2 (6.17)	154.4 (3.52)	18.3 (4.92)	211	13	57.9
10	F/61	39	71.7 (2.56)	67 (1.95)	75.6	100.9 (4.73)	153.8 (2.17)	42.6 (10)	417	3	75.7
11	M/71	71	94.5 (3.64)	70.8 (2.11)	58.4	124.3 (7.46)	178.9 (3.81)	25.6 (7.65)	572	11	68.5

FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; FEV₁/FVC: FEV₁ and FVC ratio; TLC: total lung capacity; RV: residual volume; DLCO: diffusing capacity of the lung for carbon monoxide; 6MWT: six-minute walk test; and PaO₂: arterial oxygen tension.

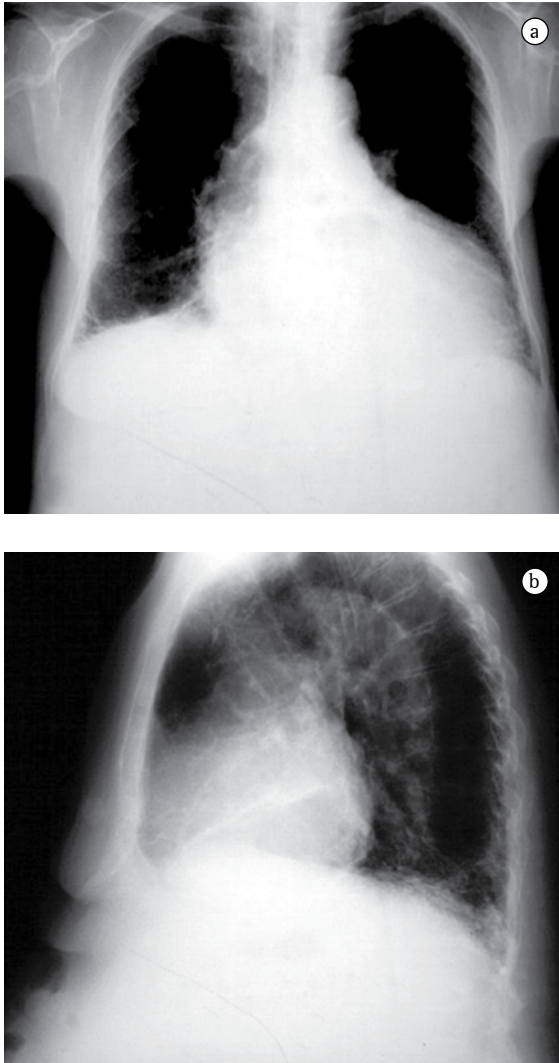


Figure 1 - Anteroposterior (a) and lateral (b) chest X-ray of a 69-year-old woman, showing hypertransparent areas and reduced vascularization in the upper lung lobes, combined with reticular pattern in the lower lobes, as well as heart enlargement due to right heart enlargement.

All patients underwent transthoracic echocardiography. Due to the absence of tricuspid regurgitation, the pulmonary artery systolic pressure (PASP) could not be estimated in 4 patients. In those patients, the mean right ventricle diameter was 1.7 ± 0.3 cm. Of the remaining 7 patients, 3 presented PSAP ≤ 35 mmHg. In the other 4 cases, PSAP was > 35 mmHg (mean, 61.8 mmHg; range, 36–84 mmHg). In those 4 cases, the mean right ventricle diameter and the mean tricuspid regur-

gant jet velocity were, respectively, 3.6 ± 1.6 cm and 3.7 ± 0.9 m/s. Clinical signs of *cor pulmonale* were present in 2 patients, who were submitted to right heart catheterization, demonstrating PSAPs of 55 and 48 mmHg, respectively (the PSAP estimated by echocardiogram was 85 and 84 mmHg, respectively). Of those 2 patients, 1 evolved to death due to acute *cor pulmonale* and respiratory failure.

Eight of the patients were submitted to bronchoscopy. The bronchoscopic findings and the bronchoalveolar lavage results (tests for bacteria, fungi and acid-fast bacilli) were normal in all cases. In 3 patients, TBB demonstrated normal respiratory mucosa. In the other cases, the TBB findings were peripheral lung parenchyma with signs of previous and recent hemorrhage; small organizing focus; peripheral lung parenchyma with area of fibrosis and smooth muscle hyperplasia; and peripheral lung parenchyma without alterations. One patient did not undergo TBB, and 2 patients did not undergo bronchoscopy because they were lost to follow-up. At this writing, 1 patient was awaiting bronchoscopy.

Discussion

In this study, we have reported clinical and functional findings in 11 patients who presented, simultaneously, emphysema in the upper lung lobes and fibrosis in the lower lung lobes, resulting in a mixed pattern in pulmonary function tests. In the concomitance between these two diseases, FEV₁ and FEV₁/FVC ratio can be normal or consistent with mild obstruction or restriction, with relatively preserved pulmonary volumes and a significant decrease in DLCO. In such patients, PH and hypoxemia can occur at rest or upon exertion.

The hyperinflation and the high compliance in the emphysematous areas compensate for the volume loss due to fibrosis, resulting in normal or slightly altered pulmonary volumes. In emphysema, due to the progressive destruction of the alveolar structures, DLCO is reduced. In IPF, the decreased DLCO occurs due to a reduction in the pulmonary capillary volume and abnormalities in the ventilation-perfusion ratio.⁽¹⁸⁾ Therefore, the combination of emphysema and IPF might have an additive or synergic effect on DLCO, reducing it to the point that hypoxemia results. In patients with IPF, emphysema, even emphysema that is limited in its extent (mean, 14% of the total pulmonary volume

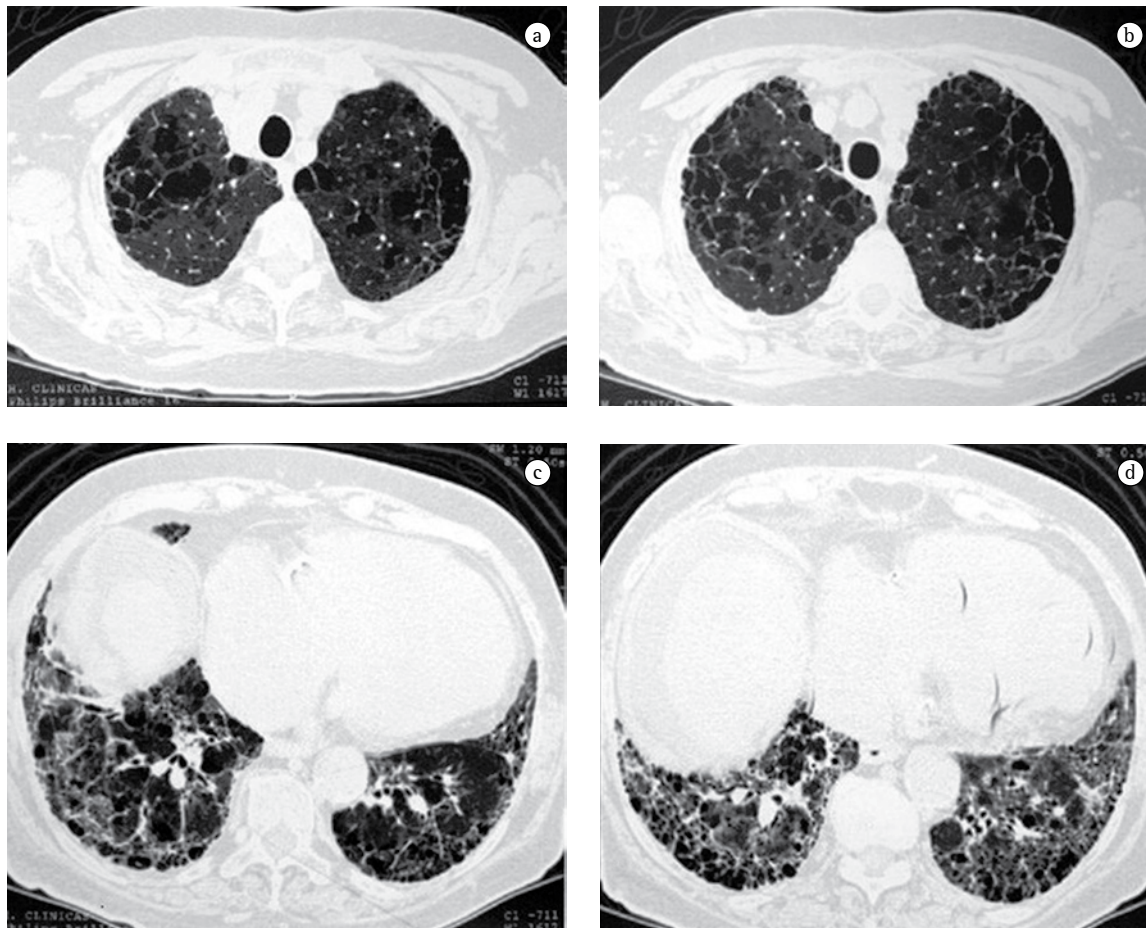


Figure 2 - High-resolution computed tomography slices of the chest showing emphysema in the lung apices (a and b) and fibrosis, including honeycombing, in the lower regions of the lung (c and d).

in a sample of 21 such patients), has been associated with the worsening of pulmonary function test results.⁽¹⁹⁾ Recently, a retrospective study evaluated the characteristics of patients who presented decreased DLCO as unique alteration in pulmonary function tests. The most frequent diagnosis in these case series studies was the combination of emphysema and IPF.⁽²⁰⁾

The cases described in this study are similar to those reported in previous studies.^(9,19,21,22) Most of our patients presented normal spirometry findings or mild obstruction, together with normal pulmonary volumes. All of the patients presented reduced DLCO. Of the 10 patients taking the six-minute walk test, 9 presented hypoxemia during exercise.

In one study,⁽²¹⁾ the characteristics of 21 patients with IPF and preserved pulmonary volumes (defined as FVC > 80%) were compared with those of 27 patients with IPF and pulmonary restriction. In the group of patients presenting preserved volumes, there was a greater proportion of males, of smokers and of individuals diagnosed with emphysema compared with the group of patients presenting pulmonary restriction. However, computed tomography scans were used to document the concomitant presence of emphysema in only 9 of the 21 patients. All of the patients evaluated in our study presented HRCT findings consistent with IPF and emphysema.

In a retrospective multicenter study, 61 patients diagnosed with concomitant emphysema and IPF

were evaluated. All were smokers and presented dyspnea on exertion. Pulmonary volumes were normal in 75% of the patients. The prevalence of pulmonary hypertension was 47% at diagnosis and 55% during follow-up. The patients were monitored for 2.1 ± 2.8 years after the diagnosis. The presence of PH at diagnosis was identified as an important prognostic factor in that case series study.⁽²²⁾ In our study, 4 of the 11 patients (36.4%) who underwent echocardiogram presented PH at diagnosis, which was confirmed by heart catheterization in 2 cases.

In our study, all of the patients were smokers. Smoking is responsible for most cases of pulmonary emphysema⁽¹⁸⁾ and might be an independent risk factor for IPF.⁽⁸⁾ Active smoking in patients with IPF has been shown to be associated with higher values of residual volume and functional residual capacity, as well as with a greater decrease in DLCO.⁽²³⁾ Although the mechanism involved in the combination of emphysema and IPF remains unknown, studies suggest that smoking may be the common etiologic factor. The use of tobacco increases the release of tumor necrosis factor alpha (TNF- α) in the lungs. In one animal model, overexpression of TNF- α was found to lead to pathological features consistent with emphysema and IPF.⁽²⁴⁾ The results of another study suggested that the same pathogenetic pathway is associated with the genesis of these two diseases.⁽²⁵⁾

In our study, 8 patients presented digital clubbing. It is known that this finding is unrelated to emphysema. Digital clubbing that arises in adulthood, especially in a smoker, is suggestive of lung cancer. However, postinfection bronchiectasis or diagnosis of associated interstitial disease, such as in the case of our patients, are causes that should be considered in the differential diagnosis of digital clubbing in a patient with COPD.

Our study has limitations that need to be considered. The main limitation is that the cases were retrospectively identified in an active search among patients treated in the outpatient clinics specialized in interstitial lung diseases and COPD in our hospital. Retrospective studies can be biased in terms of selection (cases lost to follow-up), as well as measurement (data obtained from medical charts). Some tomographic findings, such as reticular opacities and traction bronchiectasis, were reported at a lower-than-expected frequency. Since the tomographic alterations were described using

patient charts, it is possible that they do not reflect the real occurrence of findings. Another aspect that needs to be considered is that none of our patients underwent surgical lung biopsy to confirm the diagnosis. In some cases, the tomographic findings were typical, and surgical biopsy would have provided little benefit. Other patients refused to undergo this procedure. It should also be borne in mind that this procedure carries significant risk. In the largest study of patients with emphysema and IPF reported in the literature,⁽²²⁾ only 8 of the 61 patients evaluated were submitted to surgical biopsy. In the other case series studies,^(9,19,21) none of the patients underwent such procedure. Finally, bronchoscopy with TBB or BAL to exclude alternative diagnoses was not performed in 3 patients who were lost to follow-up. In the same study mentioned above,⁽²²⁾ BAL was performed in only 27 of the 61 patients evaluated.

We conclude that the concomitant presence of emphysema and IPF should be acknowledged as an entity with its own characteristics, in which there is a discrepancy between the spirometry findings and the DLCO. The opposing effects that these diseases have on elastic recoil, leading to the preservation of pulmonary flows and volumes, might cause this association to go unnoticed. However, the significant decrease in DLCO, the moderate-to-severe PH, and hypoxemia on exertion demonstrated the severity of this combination. Although the concomitance of emphysema and IPF can be an incidental finding, evidence suggests that smoking induces both diseases in the same patient.

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