Combined Pulmonary Fibrosis and Emphysema

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Introduction

Combined pulmonary fibrosis and emphysema (CPFE) is a distinct clinical entity characterized by the simultaneous coexistence of both upper lobe emphysema and lower lobe pulmonary fibrosis. Although it was first described in 1990, it has not received enough recognition. Due to its unique lung function and clinical profile, pulmonologists should be aware of its existence while evaluating patients with pulmonary fibrosis.

Case Summary

Our patient was a 70-year-old Hispanic male, referred for evaluation of progressive shortness of breath. According to the patient, he was in his usual state of health until the year before, when he started getting short of breath with exertion. Initially, dyspnea occurred only with severe exertion, but it progressively got worse, to the point where the patient was getting short of breath even with mild exertion and sometimes at rest. Over the last year he also had a persistent dry cough, and his exercise tolerance had dramatically decreased, to less than a block. He had been using albuterol inhaler prescribed by the primary care physician, without any symptomatic relief. He denied any paroxysmal nocturnal dyspnea, chest pain, fever, or hemoptysis.

Past medical history included benign prostatic hyperplasia, and he denied any surgical history. Social history was positive for 40 pack-year smoking, and he quit 3 years ago. He denied any alcohol or drug abuse. He worked as a laborer all his life, including occasional painting and marble cleaning jobs. He also denied any travel history or having any pets. Influenza and pneumococcal vaccines were up to date. Physical exam revealed a moderately built Hispanic male in mild distress. Vital signs were normal except for a low oxygen saturation of 92%. Pertinent positives were inspiratory crackles and substantial clubbing. On 6-min walk test he walked only 200 m (normal predicted 6-min walk distance for him was around 600 m) and desaturated to 82%. Peak expiratory flow was 550 L/min.

Chest x-ray showed bilateral lower lobe pulmonary fibrosis (Fig. 1). High-resolution computed tomogram (HRCT) showed lower lobe subpleural honeycombing, along with fibrosis and traction bronchiectasis (Fig. 2) and bilateral upper lobe paraseptal emphysema with bullae (Fig. 3). Pulmonary function tests interestingly showed no restrictive or obstructive pattern; rather, they showed preserved lung volumes with severely decreased diffusing capacity (Table 1).

The rest of the basic lab work was normal, including a negative human immunodeficiency virus test and rheumatologic workup. Echocardiogram showed moderate pulmonary hypertension (PH), with a right ventricular systolic pressure of 50 mm Hg. Based on the clinical presentation and workup, a diagnosis of CPFE was made, and surgical lung biopsy was not pursued. He was offered oxygen for symptomatic relief, which the patient refused.

Discussion

CPFE, a distinct clinical entity characterized by the simultaneous coexistence of upper lobe emphysema and lower lobe pulmonary fibrosis, was first described by Wiggins et al in 1990.[1] Unique to this form of idiopathic pulmonary fibrosis (IPF) is the preserved lung volumes, due to the opposing effects of both emphysema and fibrosis on the total lung volume. In contrast, the combination has an additive effect on impairing gas exchange, resulting in a significantly reduced diffusing capacity in CPFE, compared to either entity alone. Since its initial description, CPFE has eventually been reported in a few case series and case reports.[2-7]

As first described by Wiggins et al and further reinforced in later case series, CPFE seems to occur mostly in males past their sixth decade. The underlying cause for

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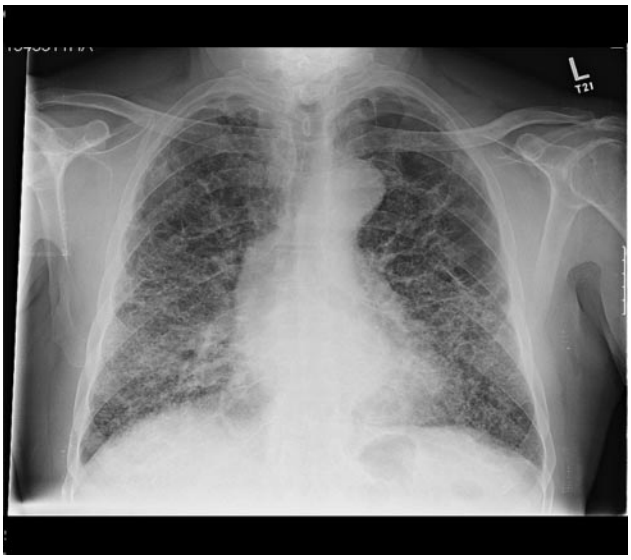

Fig. 1. Chest x-ray show bilateral lower lobe pulmonary fibrosis.

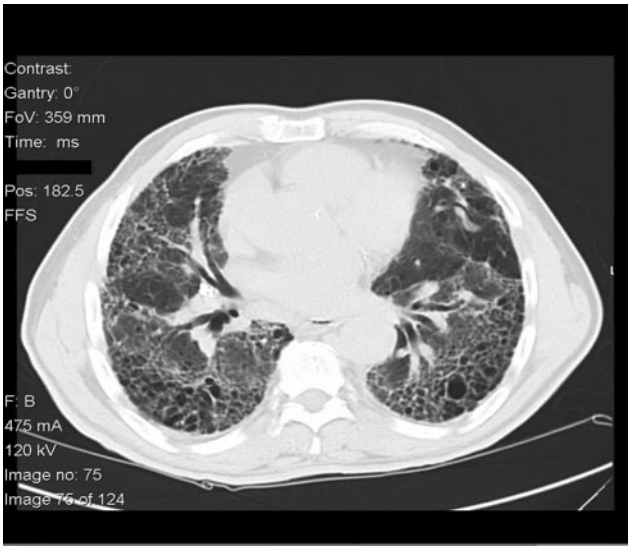

Fig. 2. High-resolution computed tomogram shows lower lobe subpleural honeycombing, fibrosis, and traction bronchiectasis.

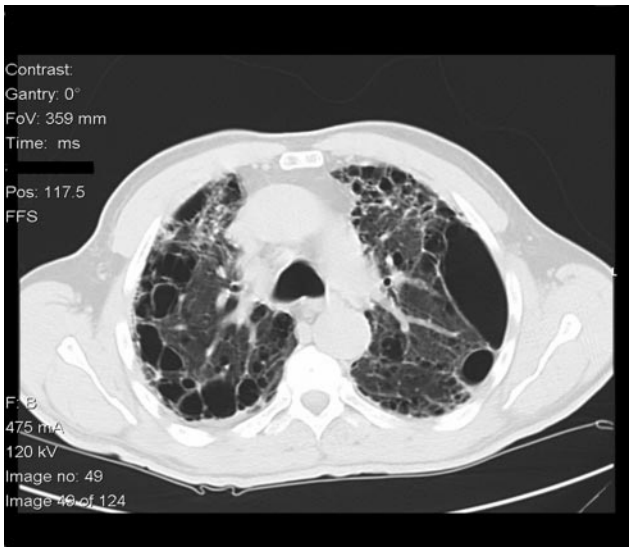

Fig. 3. High-resolution computed tomogram shows bilateral upper lobe paraseptal emphysema with bullae.

Table 1. Pulmonary Function Tests*

	September 2009	July 2010
FEV_1	2.79 (107)	2.53 (100)
FVC	3.45 (91)	3.13 (84)
FEV_1/FVC	81	80
MVV	136 (130)	109 (105)
TLC	6.91 (114)	4.80 (80)
VC	3.38 (89)	3.19 (85)
RV	3.54 (157)	1.60 (71)
FRC	3.93 (115)	2.25 (67)
D_{LCO}	8.62 (36)	5.77 (24)

* Values in parentheses are percent of predicted.
MVV = maximum voluntary ventilation
TLC = total lung capacity
VC = vital capacity
RV = residual volume
FRC = functional residual capacity
D_{LCO} = diffusing capacity of the lung for carbon monoxide

CPFE has not been established. Smoking is a consistent risk factor shown to be associated with CPFE. Smoking is presumed to trigger upper lobe emphysematous changes in certain IPF patients, resulting in this distinct clinical entity. Barnhart et al also showed that in asbestos workers with underlying interstitial fibrosis, the group that smoked had preserved lung volumes, supporting the assumption that smoking has something to do in the development of CPFE.[8] Moreover traction of the emphysematous upper zones by the fibrosed lower zones leads to the development of massive bullae that are also typical of CPFE. Other than smoking, an underlying genetic susceptibility and/or an environmental trigger cannot be completely excluded. Lundblad et al showed that in transgenic mice tumor necrosis factor alpha overexpression, driven by the surfactant protein C promoter, induced the pathologic changes consistent with both emphysema and pulmonary fibrosis.[9] Daniil et al showed a significant association with agrochemical compound exposure in their series of CPFE patients.[10]

CPFE patients classically present with progressive shortness of breath, with the average duration of symptoms for about 3 years before diagnosis.[4] On examination, patients usually have inspiratory dry crackles from the underlying pulmonary fibrosis, and a substantial number of them also have digital clubbing. HRCT of the chest is the imaging of choice in making a diagnosis of CPFE.[1] HRCT typically

shows the characteristic upper lobe paraseptal emphysema with bullae and lower lobe subpleural honeycombing with interstitial fibrosis and traction bronchiectasis. The upper lobe emphysema is usually not well appreciated on regular chest x-rays. Surgical lung biopsy is usually necessary for making a confident clinicopathologic diagnosis of basal IPF. However, with the classic clinical picture and HRCT findings, a confident diagnosis of IPF can be made by an experienced pulmonologist and radiologist, without the need for a surgical lung biopsy.[11,12] Pathology shows the characteristic usual interstitial pneumonia pattern in most patients; nevertheless, other forms of idiopathic interstitial pneumonias, like fibrotic variants of non-specific interstitial pneumonia, desquamative interstitial pneumonia, cryptogenic organizing pneumonia , and other smoking related interstitial lung diseases, may also be seen.[6,13] Once the diagnosis of IPF is made, CPFE can be recognized as a distinct entity by the simultaneous presence of upper lobe emphysema.

With regard to how the yearly pulmonary function test parameters change in CPFE, Akagi et al showed that, compared to IPF alone patients, the CPFE group of patients had a significantly higher baseline percent-of-predicted vital capacity, a lesser yearly rate of decline in percent-of-predicted vital capacity, a lower baseline FEV_1/FVC, with a tendency to decrease with time and a lower baseline diffusing capacity.[14] In contrast, Kitaguchi et al showed that, compared to COPD only patients, the CPFE group of patients had milder air-flow limitation, lower diffusing capacity, more severe desaturation during 6-min walk test, and more of paraseptal emphysema on HRCT.[15] Serial pulmonary function tests of our patient are shown in Table 1, for comparison. Although his pulmonary function tests are showing a trend toward restrictive pattern, lung volumes are relatively preserved.

Unfortunately, there are not many treatment options available for this grave syndrome.[12] Corticosteroids, immunosuppressive agents, and antifibrotic agents offer little to no benefit. Home oxygen can be offered for symptomatic relief. Lung transplant, which has been shown to offer some survival advantage in IPF patients, may also be considered as an option in CPFE.[12] Like IPF, CPFE also has an overall poor prognosis. The risk of developing PH is between 50–90% in CPFE.[4,16] Cottin et al showed a prevalence of PH in 47% of CPFE patients at diagnosis, and in 55% during follow-up.[4] Hypoxic pulmonary vasoconstriction and a reduced capillary bed due to the underlying emphysema and fibrosis may explain the eventual development of PH. Presence of PH at diagnosis was by itself shown to be a key determinant of poor prognosis. Mejia et al showed that a pulmonary artery pressure > 75 mm Hg was associated with increased mortality.[16] In fact, the 5 year survival rate was shown to be 25% for patients with PH, versus 75% for those without PH.[4] In addition to PH, lower cardiac index, lower diffusing capacity, FVC $< 50\%$ predicted, and a longitudinal decline in FEV_1 have been shown to be associated with poor prognosis.[16-18]

CPFE patients may also have a higher prevalence of lung cancer (42–46%), with squamous cell carcinoma being the most common histologic type.[15,19] With regard to the follow-up of CPFE patients, it is important to notice that, unlike IPF patients, where we follow yearly deterioration in lung volume, we cannot do so with CPFE patients, due to their relatively preserved lung volumes. This brings up an important question: should CPFE patients be excluded from future research involving IPF, due to their distinctive clinical and pulmonary function profile? The median survival of CPFE patients ranged between 2–6 years, but it is not clear at this time if CPFE has a better or worse mortality, compared to IPF alone, due to inconsistent and insufficient literature.[4,13,14,16]

CPFE is a rarely recognized clinical entity that pulmonologists should be aware of and should consider in their differential diagnosis when assessing patients with isolated severe impairment in their diffusing capacities out of proportion to their total lung volumes. Further research is essential in understanding the etiology and pathophysiology of this unique syndrome. The question remains whether the development of both fibrosis and emphysema simultaneously is simply a coexistence of 2 independent diseases or whether there is a shared pathway in certain individuals that result in both fibrosis and emphysema after exposure to cigarette smoke or other environmental factors. It is also unknown, at this time, if aggressive management of the underlying emphysema would have any sort of beneficial effect on CPFE.

Teaching Points

- CPFE is a distinct clinical entity characterized by the simultaneous coexistence of both upper lobe emphysema and lower lobe pulmonary fibrosis.
- Unique to CPFE is the preserved lung volumes in spite of substantially reduced diffusing capacity.
- CPFE is seen mostly in elderly males with substantial smoking history.
- CPFE has a progressive course, with an average duration of symptoms of about 3 years before diagnosis.
- HRCT is the imaging of choice, and it typically shows the characteristic upper lobe paraseptal emphysema with bullae, and lower lobe subpleural honeycombing with interstitial fibrosis and traction bronchiectasis.
- Surgical lung biopsy is usually necessary to make a confident clinicopathologic diagnosis of CPFE, and pathology shows the characteristic usual interstitial pneumonia pattern in most patients. However, with the clas-

sic clinical and HRCT findings, a confident diagnosis can be made without the need for a surgical lung biopsy.

- Unfortunately, CPFE has no effective treatment options available, other than possible lung transplant, and overall has a grim prognosis.
- The prevalence of PH is high in CPFE, and its presence at diagnosis is by itself a poor prognostic sign.

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