

The worst of both worlds-combined pulmonary fibrosis and emphysema syndrome

Sheeba Habeeb Ba Aqeel¹, Abhishek Biswas², Peruvemba S. Sriram²

¹Deccan College of Medical Sciences, Hyderabad, India; ²Division of Pulmonary, Critical Care and Sleep Medicine, University of Florida, Gainesville, USA

Correspondence to: Abhishek Biswas, MD. Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, 1600 SW Archer Road, Room M452, PO Box 100225, Gainesville, FL 32610-0225, USA. Email: abiswas@ufl.edu.

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Introduction

Rarely, we will see patient in our practice who might appear to have a combination of two different disease belonging to opposing ends of a spectrum of clinical features. Combined pulmonary fibrosis and emphysema syndrome (CPFE) is one of such rare conditions where the physician encounters a mix of clinical features which are thought to be inconsonant. These patients have a variable mix of pulmonary fibrosis and emphysema and a very different course compared to patients with either disease alone.

Case presentation

We present a case of a severely dyspneic 63-year-old man with features of both emphysema and pulmonary fibrosis. He was diagnosed with emphysema four years back and has been using two liters of oxygen till eight months back when he started getting more short of breath and had a rapid increase in his oxygen requirement. He is an ex-smoker with a 30-pack year smoking history and quit smoking seven years back. He is a mechanical engineer by profession, has a history of exposure to asbestos but denied any exposure to birds, chemicals or molds. He does not have any pets at home or any significant travel history. He denied any fevers, chills, hemoptysis, or chest pain. On evaluation, he was hypoxic on 6 L of oxygen and was desaturating to the high 80 s even with mild exertion. The patient was afebrile, normotensive, sitting up in a chair at the time of initial assessment. He had a regular tachycardia



Figure 1 Chest X-ray demonstrating prominent bilateral lower lobe predominant interstitial fibrosis.

of 101 beats/min and a respiratory rate of 28 breaths/min. Auscultation of the lungs revealed basal inspiratory crepitation with prolonged expiratory wheezes scattered throughout both lung fields. He had grade III clubbing bilaterally. Examination of other organ systems was unrevealing. Initial chest X-ray revealed bilateral diffuse interstitial fibrosis more prominent in the periphery of the lungs. Bilateral apical pleural thickening was also noted (*Figure 1*). CT of the chest demonstrated extensive ground glass opacities with centrilobular emphysematous changes at the apices (*Figure 2*). Bilateral lower lobe predominant fibrosis with honeycombing and traction bronchiectasis were also noted (*Figure 2*). A thick walled cystic lesion (TWCL) was present in the lower lobe (*Figure 3*).

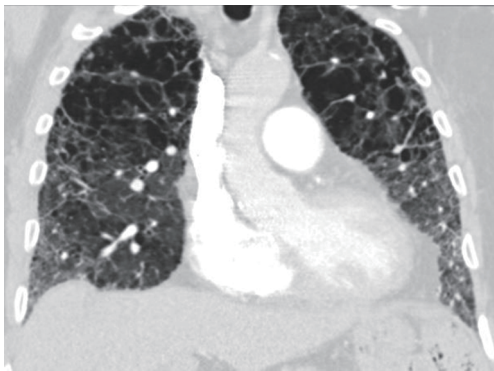


Figure 2 A coronal section CT scan of the lung demonstrates bilateral diffuse lower lobe predominant interstitial fibrosis and ground glass changes. There are multiple hyperlucent cystic air spaces indicative of emphysema in both the upper lobes.

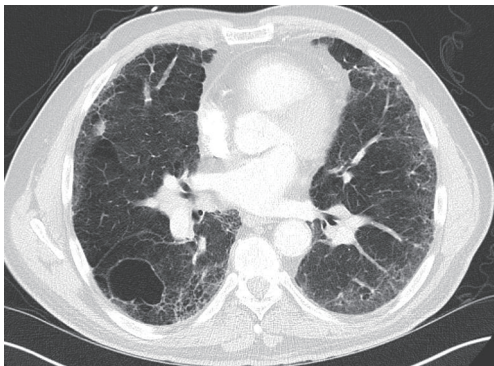


Figure 3 CT scan of the lung (axial section) at the level of the lower lobes demonstrates a thick walled cystic lesion (TWCL) in the right lower lobe along with honeycombing in the posterior-basal segment of the same lobe. There is prominent diffuse interstitial fibrosis throughout both lungs.

Pulmonary function tests (PFT) demonstrated mild obstruction with severely reduced diffusion capacity for oxygen (DLCO) (*Figure 4*). His echocardiogram revealed ejection fraction of 50–55%, right ventricular systolic pressure of 35–40 mmHg with evidence of left ventricular diastolic dysfunction. Laboratory studies demonstrated a leukocyte count of 10.2 thousand/mL with 73% granulocytes, hemoglobin of 17.4 gm/dL, and a normal metabolic panel. Immunological work up was unrevealing with a negative antinuclear, anti-double stranded DNA, anti-neutrophil cytoplasmic, rheumatoid factor, anti-SSA/Ro and anti-La/SSB, anti-scleroderma, anti-cyclic citrullinated peptide and anti-Jo 1 antibodies.

Discussion

There are two clinical scenarios that could explain this unusual mix of findings. This could either represent preexisting emphysema with superimposed pulmonary fibrosis or vice-versa i.e., preexisting pulmonary fibrosis with superimposed emphysema. There also exists a third possibility, one which fits best with this particular clinical presentation and imaging features, appropriately termed the syndrome of CPFE. This syndrome was first described by Cottin *et al.* in 2005 (1). In the absence of a consensus definition, we can use certain clinical characteristics to help us identify this syndrome (2):

- (I) Male (9:1; M:F);
- (II) Heavy smoker;
- (III) Severely symptomatic;
- (IV) Characteristic PFT with isolated reduction in DLCO;
- (V) High incidence of pulmonary hypertension (PH);
- (VI) Have a high incidence of lung cancer.

There is a lack of clear epidemiological data to clarify the prevalence of this syndrome. A review of IPF literature indicates that between 8% to 51% of CT scans from patients with idiopathic pulmonary fibrosis (IPF) demonstrates some degree of emphysema (3,4). Similarly, review of lung imaging data among those diagnosed with emphysema shows that 4.4% to 8% of patients have some degree of lung fibrosis (5,6). The importance of identifying this condition lies in the fact that up to 35% of patients with IPF may actually have CPFE and thus may have a different clinical course than patients with IPF alone (2). These patients depend on compensatory hypoxic vasoconstriction to modify their ventilation/perfusion mismatch and attempt to preserve normoxemia which puts them at risk of having a paradoxical hypoxemic response to commonly utilized pulmonary vasodilator therapies with prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase inhibitors aimed at treating PH in such patients (7). Patients with CPFE are at a high risk of developing lung cancer and require annual surveillance CT scans (8) and also need to be referred for lung transplant earlier than somebody with similar degree of emphysema or fibrosis alone. With a normal to near normal FEV1, their BODE (Body-mass index, airflow Obstruction, Dyspnea, and Exercise) indexes are falsely low and do not accurately reflect the severity of their condition. Thus BODE scores are not an accurate way of assessing candidacy for lung transplant among such patients. Quite clearly, those with CPFE have a disease that has a different

Arterial Blood Gases

	pH	PaCO ₂	PaO ₂	HCO ₃	O ₂ Sat	FiO ₂
Pre Drug	7.40	40.00	43.00	25.00	78.00	21.00
	Hgb	HbO ₂	COHb	METHb		
Pre Drug	18.70					

Spirometry

	Units	Pre Drug Reported	Pre Drug % Predicted	Predicted	Post Drug Reported	Post Drug % Predicted	% Change
FVC	L,btps	4.36<	80<	5.48			
FEV1	L,btps	2.93<	72<	4.10			
FEV1/FVC	%	67	90	75			
FEFmax	L/s	9.17	92	9.99			
FEF25-75%	L/s	1.44	45<	3.21			
FEF25%	L/s	8.60					
FEF50%	L/s	2.26					
FEF75%	L/s	0.57					
MVV	L/min,btps	123.21	90	136.18			
BP	mmHg	762					
Plmax/MIP	cmH ₂ O			-75.05			
PEmax/MEP	cmH ₂ O			120.85			

Lung Volumes, Body Box

	Units	Pre Drug Reported	Pre Drug % Predicted	Predicted	Post Drug Reported	Post Drug % Predicted	% Change
VC	L,btps	4.44	81	5.48			
IC	L,btps	2.94	70<	4.22			
ERV	L,btps	1.51	120	1.26			
FRC	L,btps	3.78	96	3.95			
RV	L,btps	2.27	84	2.70			
TLC	L,btps	6.72	82	8.17			
RV/TLC	%	34	103	33			
VTG	L,btps	3.92					
RAW	cmH ₂ O/L/s			1.11			

Lung Volumes (DL)

	Units	Pre Drug Reported	Pre Drug % Predicted	Predicted	Post Drug Reported	Post Drug % Predicted	% Change
VC	L,btps			5.48			
IC	L,btps			4.22			
ERV	L,btps			1.26			
FRC	L,btps			3.95			
RV	L,btps			2.70			
TLC	L,btps			8.17			
RV/TLC	%			33			

Diffusion Capacity

	Units	Pre Drug Reported	Pre Drug % Predicted	Predicted	Post Drug Reported	Post Drug % Predicted	% Change
Dsb	ml/min/mmHg, stpd	6.96<	20<	34.06			
DsbHb	ml/min/mmHg, stpd	6.33<	19<	34.06			
VAsb	L,btps	5.39	68<	7.98			
D/VAsb	ml/min/mmHg/L, stpd	1.29	30<	4.27			
Hgb	g/dl	18.70					

Figure 4 Pulmonary function test demonstrating mild obstruction (FEV1/FVC ratio of 0.67; normal is greater than 0.80) with FEV1 at 72% predicted. Lung volumes appear normal. The diffusion capacity for oxygen appears disproportionately low at 19% predicted when corrected for hemoglobin (80% predicted is considered normal).

clinical course from those patients with IPF and COPD and hence, trials on treatment for COPD and IPF have always excluded patients with CPFE.

The identification of CPFE requires the physician to be familiar with radiological findings in both interstitial lung diseases and emphysema. A mix of all three types of emphysema are noted in the upper lobes with centrilobular emphysema (97%) being the most common followed by paraseptal emphysema (93%) and bullae (54%) (2). Paraseptal emphysema is seen much more frequently among patients with CPFE than those with emphysema alone. This provides support for the hypothesis that paraseptal and centrilobular emphysema have different inflammatory signature, different genes and result from different responses to smoke inhalation. Thick-walled cystic lesions (TWCL) (*Figure 3*) have been increasingly recognized as unique radiological and pathological features of CPFE (9). Enlargement of TWCLs are thought to reflect the worsening of interstitial fibrosis and progression of the disease. Autopsy studies have revealed that radiological and pathological TWCLs were observed in 72.7% of the CPFE patients, but not in any patient with either IPF or emphysema alone (10). Features of pulmonary fibrosis include honeycombing which is the most common feature (75.6–95%) followed by reticulation (84.4–87%) and traction bronchiectasis (40–69%) (2,11). The degree of emphysema based on CT emphysema scores are reported to be similar to those with mild to moderate emphysema but lower than those with severe emphysema (12,13).

CPFE is thought to be the result of a poorly-understood interaction between environmental and genetic factors, among which the best recognized is cigarette smoke. A high frequency of fibrosis has been observed in pieces of lung tissue removed for tumor surgery from smokers. These patients showed no clinical evidence of interstitial lung disease (14). Kaolinite or aluminum silicate in cigarette smoke is reported to lead to macrophage accumulation after chronic inhalation and trigger a series of pathophysiological events leading to respiratory bronchiolitis-interstitial lung disease (RB-ILD) and emphysema in animal models (15). Other occupational factors such as welding (16) or exposure to talc (17) have been reported to be associated with CPFE. CPFE syndrome has been described in a series of patients with connective tissue diseases (CTD), mainly among smokers or former smokers with rheumatoid arthritis and systemic sclerosis. Mutation in the following genes has been reported to result in the development of CPFE.

- (I) Surfactant protein C (SFTPC) gene (18);
- (II) ABCA3 mutation (19);

- (III) Mutations in the essential telomerase genes (hTERT or hTR is a risk factors for pulmonary fibrosis in up to one-fifth of familial cases). Association between CPFE and mutation in the hTERT gene has been reported in several individuals of a family with the CPFE phenotype (20).

Management

CPFE syndrome is associated with poor survival statistics, worse than those with pulmonary fibrosis or emphysema alone. A five-year survival of only 35–80% and a median survival ranging between 2.1 to 8.5 years have been reported (1,2). The major causes of death in CPFE are chronic respiratory failure, PH, acute exacerbation and lung cancer. One of the reasons for this low survival rates is the lack of clear management guidelines for such patients combined with the fact that these patients develop life threatening complications earlier than those with pulmonary fibrosis or emphysema alone. Patients with CPFE are excluded from trials on IPF and COPD, and as a result, the usefulness of newer therapies in such patients is understudied. However, oxygen therapy, smoking cessation, inhaled bronchodilators should be prescribed for these patients as usual. Corticosteroids should be used for patients with CTD related CPFE (CTD-CPFE) and they usually have better clinical outcomes than non CTD-CPFE patients (9). The major complications of CPFE that have a profound impact of survival statistics described earlier are as follows:

- (I) Pulmonary arterial hypertension (PH): the prevalence of PH has been reported to be more common in patients with CPFE (47% to 90%) than in patients with emphysema (10% to 30%) and advanced IPF (31% to 46%) (21,22). One-year survival rate of only 60% was reported in a study involving 40 CPFE patients with PH confirmed by right heart catheterization (23). Unfortunately, the impact of using pulmonary vasodilators has not been extensively studied and a possibility of worsening hypoxemia exists due to ventilation-perfusion mismatch resulting from such treatment (7);
- (II) Lung cancer: patients with CPFE develop lung cancer more commonly (35.8% to 46.8%) than patients with IPF (22.4% to 31.3%) and those with emphysema alone (6.8% to 10.8%) (10,24). Interestingly, squamous cell carcinoma being the most common histologic type of cancer in these patients (24). Lung cancer in patients with CPFE

and IPF predominantly occurs in the sub-pleural areas unlike those with COPD where it occurs more frequently in the lung apices (24). This distribution suggests that the emphysema by itself might not contribute as much as lung fibrosis to the development of lung cancer in CPFE;

- (III) Acute lung injury: a very high incidence of acute lung injury after lung resection surgery or chemotherapy has been noted and up to 70% of post-lobectomy ARDS cases (70%) were noted to have preexisting CPFE (25). A 19.8% incidence of acute lung injury following definitive lung cancer therapy was reported among 101 patients with CPFE and lung cancer. Surgical resection was the most common cause of acute exacerbation (27.3%) followed by chemotherapy (20%) and radiation (16.7%) alone (26).

In view of such poor survival data associated with this syndrome and the lack of a definitive management strategy, it is reasonable to offer lung transplantation to all patients with CPFE as soon as they are diagnosed (27). Our patient underwent a rapid pre-transplant workup and has undergone a successful double-lung transplantation one week ago.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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