

Diagnosis and Treatment of Combined Pulmonary Fibrosis and Emphysema in 2022

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Chronic obstructive pulmonary disease (COPD) affects an estimated 6.4% and interstitial lung disease (ILD) affects an estimated 0.3% of adults in the US. COPD is defined by airflow obstruction on spirometry, as indicated by a low ratio of forced expiratory volume in the first second to forced vital capacity. Emphysema and chronic bronchitis are the main processes underlying airflow obstruction in COPD. Emphysema is visualized on chest computed tomography (CT) as foci of decreased lung attenuation due to alveolar tissue loss and results in increased lung compliance and volume (hyperinflation). In contrast, most ILDs cause fibroinflammatory parenchymal infiltration that reduces lung compliance and volumes, resulting in a restrictive ventilatory defect on pulmonary function testing. CT findings that indicate ILD include ground-glass/reticular opacities, traction bronchiectasis/bronchiolectasis, or honeycombing.

Approximately 5% of patients with COPD have ILD, resulting in *combined pulmonary fibrosis and emphysema* (CPFE).¹ Although this phenomenon has been recognized for more than 30 years, the term CPFE was coined in 2005 for idiopathic pulmonary fibrosis (IPF) in patients with preexisting emphysema. A similar phenomenon has been reported in an increasing number of patients with COPD and other ILDs, including non-IPF idiopathic interstitial pneumonias, connective tissue disease-related ILD, and fibrotic hypersensitivity pneumonitis.² The pathogenesis/pathophysiology of CPFE remains unclear. A review of publications from May 1990 to September 2020 reported that 890 patients with CPFE had been described in medical literature.³ However, it is likely that CPFE is underrecognized and underreported.^{3,4} A 2016 study identified "interstitial lung abnormality," including ground-glass or reticular abnormalities, architectural distortion, traction bronchiectasis or bronchiolectasis, honeycombing, and nonemphysematous cysts on chest CT in 4% to 9% of cigarette smokers, who often do not have clinically diagnosed ILD. These interstitial lung abnormalities were associated with a greater risk of all-cause mortality (5%-23% higher absolute mortality rates; hazard ratio, 1.3-2.7).⁴

Diagnosis

CPFE is typically diagnosed in current or previous cigarette smokers, more commonly men, aged approximately 60 to 80 years. Presenting symptoms are typically gradually worsening dyspnea on exertion, chronic cough, and recurrent pulmonary exacerbations (characterized by acute worsening of respiratory symptoms). In patients with CPFE, the severity of dyspnea and functional limitations may appear out of proportion to the severity of established COPD. Lung auscultation often reveals inspiratory crackles suggestive of pulmonary fibrosis. Chest radiography typically exhibits increased interstitial markings, particularly in the lower-lung zones, without evidence of hyperinflation. Spirometry and lung volumes in CPFE may be normal or near normal because the emphysematous component of COPD and the restrictive component of ILD have opposing effects on lung compliance and forced expiratory flow. However, both COPD and ILD decrease the area of alveolar-capillary membrane through which gas

exchange occurs, resulting in severely decreased diffusing capacity of the lungs for carbon monoxide. These patients often demonstrate oxygen desaturation with exertion. In patients with severe CPFE, oxygen desaturation may occur at rest. Oxygen desaturation with exertion or low oxygen saturation at rest out of proportion to spirometry measures may be indicative of CPFE.

CPFE is diagnosed with high-resolution (thin-section) chest CT that demonstrates both emphysema (usually upper-lung predominant) and ILD (often lower-lung predominant) (Figure). Some patients with CPFE have a radiologic pattern of ILD consistent with usual interstitial pneumonia (UIP), the fibrotic pattern associated with IPF. However, nonusual interstitial pneumonia patterns may be visualized on chest CT of patients with CPFE.

Prognosis

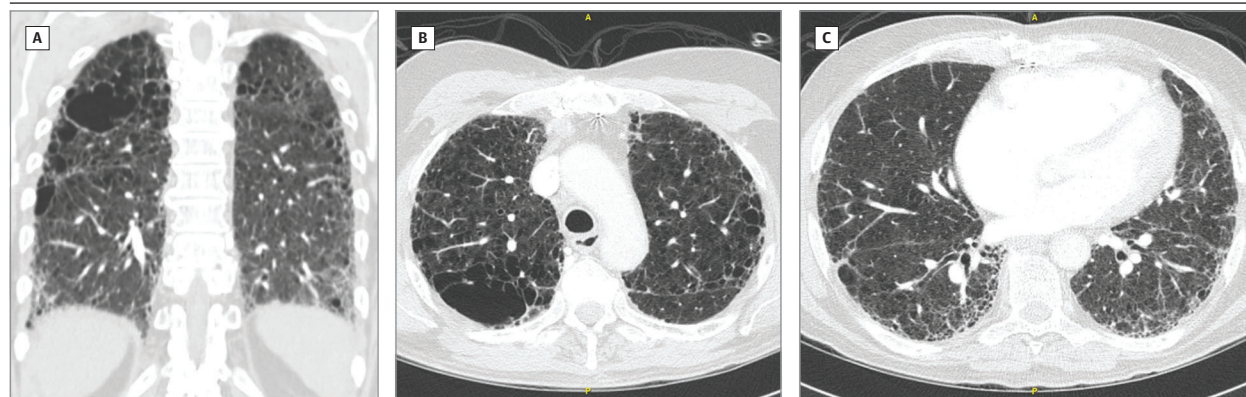
Patients with CPFE often progress to chronic respiratory failure, defined as persistent hypoxemia (partial pressure of oxygen [PaO_2] ≤ 55 mm Hg) or hypercapnia (partial pressure of arterial carbon dioxide >45 mm Hg). The clinical course of CPFE can be complicated by acute exacerbations of COPD or ILD, pulmonary hypertension (World Health Organization group 3), and lung cancer.³ Approximately 47% to 90% of patients with CPFE have pulmonary hypertension and 11% to 47% have lung cancer.³ Prognosis is associated with the severity of underlying emphysema and ILD. Patients with CPFE and IPF have decreased survival compared with patients with CPFE and other ILDs, such as hypersensitivity pneumonitis.

Treatment

Smoking cessation is important for active cigarette smokers because smoking accelerates loss of lung function (primarily indicated by declining diffusing capacity) and increases risk of lung cancer, pulmonary hypertension, and progression of ILD. Because there is no drug therapy that specifically treats CPFE, patients typically receive treatments for both the COPD and ILD components of CPFE. Treatment of COPD is guided by the severity of obstructive lung disease (based on spirometry), pulmonary symptoms, and exacerbation frequency.⁵ Although bronchodilators and inhaled corticosteroids are the primary pharmacologic therapy for COPD, patients with CPFE do not usually have airflow obstruction on spirometry; the benefits of inhaler therapy are unclear for these patients.³

Optimal management of ILD depends on accurate diagnosis, for which a multidisciplinary team (clinicians, radiologists, pathologists) is recommended.⁶ Although lung biopsy may help characterize underlying ILD in some patients with CPFE, procedure-related risks, such as acute exacerbation (COPD or ILD) and prolonged ventilator dependence, must be considered, particularly for those with severe pulmonary impairment. For IPF and other fibrotic ILDs, antifibrotic therapy with nintedanib or pirfenidone may slow progression of parenchymal fibrosis by approximately 50% over 1 year and should be considered in those with progressive fibrosis, but these medications

Figure. High-Resolution Computed Tomography (CT) Imaging of Pulmonary Fibrosis and Emphysema in a 68-Year-Old Former Smoker



Pulmonary function testing showed normal results except for reduced diffusing capacity (28% predicted). A, Coronal CT showing emphysema predominantly in the upper lungs and reticular and ground-glass opacities predominantly involving lower peripheral lung zones. B, Axial CT showing emphysematous

changes in upper lobes. C, Axial CT showing lower peripheral lung zone-predominant fibrotic changes from idiopathic pulmonary fibrosis consisting of subpleural reticular opacities and honeycombing.

have not been specifically studied in CPFE.⁶ Immunosuppressive therapy, including glucocorticoids, is preferred for ILDs of inflammatory nature as encountered in connective tissue disease-related ILDs and hypersensitivity pneumonitis. The role of combined immunosuppressive and antifibrotic therapies is being explored for some progressive fibrotic ILDs (eg, fibrotic hypersensitivity pneumonitis, scleroderma-associated ILD). Both treatment strategies are associated with adverse effects, primarily increased risk of infections with immunosuppressive treatments and gastrointestinal/hepatic toxicities with antifibrotic agents. Inhaled treprostinil, a prostacyclin analogue that causes vasodilation, may improve exercise capacity (21-m increase in 6-min walk distance at wk 16 vs baseline) for patients with CPFE-associated pulmonary hypertension.⁷ Given the limited benefits and potential toxicities associated with available therapies, a patient-centered approach considering individual preferences and tolerances in a shared decision-making process is essential.

Patients with CPFE, similar to those with other chronic lung diseases, should be evaluated and treated for comorbidities, including heart failure, gastroesophageal reflux, obstructive sleep apnea, depression, and osteopenia/osteoporosis. In addition to smoking cessation assistance, vaccination (pneumococcal, influenza, and COVID-19) is recommended. Long-term oxygen therapy should be prescribed

for patients with hypoxemia at rest or with exercise (oxygen saturation as measured by pulse oximetry <89% or $\text{PaO}_2 \leq 55$ mm Hg).⁸ A pulmonary rehabilitation program that incorporates strength and endurance training may improve dyspnea, exercise tolerance, and quality of life in patients with CPFE.⁹ Patients younger than 70 years with severe functional impairment (forced vital capacity <50% predicted, diffusing capacity of the lungs for carbon monoxide <40% predicted, or need for supplemental oxygen at rest or with exertion) should be referred for lung transplant evaluation. Ongoing discussions with patients and families about goals of care are needed along with advance care planning that includes advance directives and establishing a health care power of attorney.

Conclusions

ILD affects approximately 5% of people with COPD, resulting in CPFE. First-line therapy for CPFE consists of smoking cessation, vaccinations, pulmonary rehabilitation, and supplemental oxygen if indicated. Pharmacologic therapies, such as inhaled bronchodilators, corticosteroids, antifibrotic agents, immunosuppressive therapies, and pulmonary vasodilators, should be tailored to the individual. Clinicians should also treat underlying comorbidities, discuss advance care planning, and regularly reassess goals of care with the patient.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: None reported.

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