Review Article

Combined pulmonary fibrosis and emphysema (CPFE): an entity different from emphysema or pulmonary fibrosis alone

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Abstract: Chronic obstructive pulmonary disease (COPD) and idiopathic interstitial pneumonias (IIP), with different radiological, pathological, functional and prognostic characteristics, have been regarded as separate entities for a long time. However, there is an increasing recognition of the coexistence of emphysema and pulmonary fibrosis in individuals. The association was first described as a syndrome by Cottin in 2005, named "*combined pulmonary fibrosis and emphysema* (*CPFE*)", which is characterized by exertional dyspnea, upper-lobe emphysema and lower-lobe fibrosis, preserved lung volume and severely diminished capacity of gas exchange. CPFE is frequently complicated by pulmonary hypertension, acute lung injury and lung cancer and prognosis of it is poor. Treatments for CPFE patients with severe pulmonary hypertension are less effective other than lung transplantation. However, CPFE has not yet attracted wide attention of clinicians and there is no research systematically contrasting the differences among CPFE, emphysema/COPD and IIP at the same time. The authors will review the existing knowledge of CPFE and compare them to either entity alone for the first time, with the purpose of improving the awareness of this syndrome and exploring novel effective therapeutic strategies in clinical practice.

Keywords: Idiopathic interstitial pneumonia (IIP); idiopathic pulmonary fibrosis (IPF); pulmonary emphysema; chronic obstructive pulmonary disease (COPD); pulmonary hypertension

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Introduction

According to the definition of emphysema, the presence of excess fibrosis has been historically excluded from the diagnosis of emphysema (1). Therefore, chronic obstructive pulmonary disease (COPD) and idiopathic interstitial pneumonias (IIP), with different radiological, pathological, functional and prognostic characteristics, have been regarded as separate entities for a long time. However, there is an increasing recognition of the coexistence of emphysema and pulmonary fibrosis in individuals. In 1990, coincidental cryptogenic fibrosing alveolitis and emphysema was first described in a series of eight patients by Wiggins *et al.* (2). In 1993, Hiwatari *et al.* reported another series of nine patients who had pulmonary emphysema followed by idiopathic pulmonary fibrosis (IPF) based on the pathological findings (3).

Whether the combination of emphysema and pulmonary fibrosis is a distinct clinical entity or not remains unknown. Some consider it as a coincidence of two smoking-related diseases in one person, comparable to the coexistence of lung cancer and COPD. However, previous data had suggested that interstitial lung abnormalities were inversely associated with emphysema in smokers (4). Actually most former smokers with IPF do not have radiographic evidence of emphysema. Likewise, most patients with emphysema/COPD do not have overt evidence of interstitial fibrosis. Therefore, the combination of pulmonary fibrosis and emphysema may be a distinct consequence of smoking that reflects unique individual susceptibilities.

In 2005, Cottin *et al.* first time put forward a defined syndrome termed "*combined pulmonary fibrosis and emphysema (CPFE)*" (5), which is characterized by heavy smoking history, exercise hypoxemia, upper lobe emphysema and lower lobe fibrosis, unexpected subnormal lung volumes and severe reduction of carbon monoxide transfer. The CPFE syndrome comprises a heterogeneous population of patients and a consistent definition of CPFE has not been put forward. High-resolution computed tomography (HRCT) is the mandatory tool to diagnose this syndrome. CPFE is frequently complicated by pulmonary hypertension, acute lung injury and lung cancer and prognosis of it is poor. Treatments for CPFE patients with severe pulmonary hypertension are less effective other than lung transplantation (6).

Identification of patients with CPFE is important because this disorder has its unique natural history. However, unfortunately CPFE has not yet attracted wide attention of clinicians and there is no research systematically contrasting the differences among CPFE, emphysema/COPD and pulmonary fibrosis alone at the same time. The authors here will review the existing knowledge of CPFE and compare it to either entity alone for the first time.

Definition

First of all, it is meaningful for us to distinguish several other terms similar to CPFE, such as emphysema, smoking related interstitial lung fibrosis (SRIF), IPF/usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP) and so on.

The term, CPFE, first described by Cottin *et al.* was defined radiographically by the presence of classic features of centrilobular and/or paraseptal emphysemas in the upper lobes and pulmonary fibrosis (mainly IPF/UIP) in the lower lobes (5). Most CPFE patients have mixed pattern on pulmonary function and marked reduction in diffusing capacity for carbon monoxide (DLco) which is associated with a high prevalence of pulmonary hypertension (7). Although most cases of CPFE likely represent the common fibrotic pattern of UIP, a few cases have been reported as showing desquamative interstitial pneumonia (DIP) or unclassified interstitial pneumonia (8). Therefore, some cases designated as CPFE may be within the spectrum of SRIF (9).

Emphysema is defined as an enlargement of the air spaces distal to the terminal bronchioles due to the destruction of the tissues forming their walls. Emphysema secondary to smoking is typically centrilobular, which commonly manifests as small, localized areas of low attenuation within the central portion of the secondary pulmonary lobule on HRCT (1). It can cause an obstructive pattern, namely COPD, due to the different structural changes occurring in the lung.

SRIF is a term used to describe chronic unclassified interstitial fibrosis that can develop in smokers. The tip-off to diagnosing SRIF is that the fibrosis is composed mostly of hyalinized, eosinophilic collagen deposition that variously thickens alveolar septa and it is associated with enlarged airspaces of emphysema as well as respiratory bronchiolitis (RB) (10). In addition, the fibrosis affects predominantly the subpleural parenchyma and often has a centrilobular distribution when present in deeper parenchyma. It is essential to differentiate SRIF from other fibrotic interstitial lung diseases (ILDs), especially UIP and NSIP (9).

IPF is a chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, characterized by progressive worsening of dyspnea and lung function and associated with a poor prognosis. It is the most common ILD with a characteristic histologic pattern of UIP, which is characterized on HRCT by the presence of subpleural and basal predominance, reticular opacities and honeycombing with or without traction bronchiectasis (11). Significant architectural distortions in the form of interstitial destruction by large areas of irregular scars, and well-formed honeycombing in a predominantly subpleural/paraseptal distribution are typical features of UIP on histopathology.

NSIP is used to describe an uncommon and previously unclassified interstitial pneumonia that is now known to be associated with collagen vascular disease, hypersensitivity pneumonitis, and drug-induced lung injury. The appearances of fibrotic NSIP on HRCT are variable but also well characterized of symmetric bilateral areas of ground-glass opacity with superimposed fine reticular opacities, with or without traction bronchiectasis, and bronchiolectasis but with no or only minimal honeycombing (12). The fibrosis of NSIP usually has a fairly diffuse distribution. Moreover, when NSIP becomes severely fibrotic, chronic inflammatory cells are usually present to some degree admixed with the collagen (9).

Epidemiology

The prevalence of emphysema was reported about 21.5 per 1,000 in the general population while that of IPF varied

from 14 to 42.7 cases per 100,000 revealing it a much rarer disease compared to emphysema (13). However, the prevalence of CPFE is still not specifically known. In reported studies, the proportion of patients with CPFE detectable on HRCT scan was present from 8% to 51% in IPF patients (14,15). This variation of prevalence in CPFE may due to different extent of emphysema evaluated by HRCT (16). Inversely, the proportion of pulmonary fibrosis was estimated about 4.4-8% in patients with emphysema by HRCT (4,17,18).

Patients with CPFE are usually older, male and with a heavy smoking history. Most of the reported studies have found heavy smoking histories in almost all the CPFE patients, suggesting that smoking may be the predominant risk factor for this disorder (19-21). There is no significant difference in smoking history between CPFE and COPD (22). However, patients with CPFE and those with COPD usually have more pack-years than those with IPF (23). A male predominance in CPFE syndrome has also been reported in many studies (14,15). This could be partially explained by greater exposure to smoking or other pathogenic factors in men than women. Although both emphysema and IPF have been proved to be more common in male smokers than female smokers (24), it does not mean that gender is an independent risk factor of CPFE. Further studies are needed to explain the gender differences in this syndrome.

Pathogenesis

The pathogenesis of CPFE has not been fully elucidated to date. It is still unclear whether emphysematous and fibrotic lesions progress independently or if one results from the other. Perhaps there are some undiscovered mechanisms, which may involve a variety of cytokines and shared signaling pathways, resulting in both emphysema and pulmonary fibrosis in genetically susceptible individuals after the exposure to environmental triggers (such as smoking).

Cigarette smoking

Smoking has been turned out to be the etiologic major risk factor for both COPD and IPF (25). In a cohort of 2,416 smokers interstitial lung abnormalities detected by HRCT scans were present in 8% subjects (4). Since a heavy history of smoking was often present in most CPFE patients in a lot of research, smoking has been considered as the predominant risk factor for CPFE as well. Animal experiments had confirmed that tobacco can lead to the occurrence of emphysema and pulmonary fibrosis simultaneously (26). Another research reported that over half of lobectomy specimens excised from smokers with lung cancer had interstitial fibrosis; these patients had no clinical evidence of ILDs and even in some of them emphysema was the only CT finding (10). However, the specific pathogenesis and process of smoking in the development of CPFE are still not clear.

Occupational exposures

In addition to tobacco exposure, other environmental exposure as a potential trigger of lung injury in the CPFE syndrome is also possible. Mineral dust exposure may account for some reported cases of CPFE. Kitaguchi *et al.* reported five CPFE patients with significant exposure to agrochemical compounds (27). Karkhanis *et al.* reported a tyre industry worker who was diagnosed with CPFE (28). Roshan *et al.* reported the CPFE syndrome occurred in a welder (29). Under the circumstances CPFE was described as an occupational disease.

Connective tissue disease (CTD)

When CPFE was first described by Cottin *et al.* in 2005, patients with CTD-associated ILDs were excluded from the study (5). However, in 2011 the CPFE syndrome was first described in a series of patients with CTDs, mainly among smokers or former smokers with rheumatoid arthritis and systemic sclerosis. Patients with CTD-associated CPFE are more likely to be women, significantly younger and tend to have less severe outcomes than their idiopathic CPFE counterparts. A lower prevalence of pulmonary hypertension in patients with CTD-associated CPFE compared with that in patients with idiopathic CPFE may account, at least in part, for the better survival observed in the former group. Imaging and pulmonary function features are also similar to those in idiopathic CPFE but differ from those of CTD-associated ILD. Consequently, the syndrome of CPFE may represent a novel and unrecognized pulmonary manifestation within the spectrum of CTD-ILDs. In a recent research, elevated serum antinuclear antibodies with or without positive p-ANCA were found frequent in CPFE patients compared with IPF patients. Patients with CPFE and positive autoimmune markers exhibit a greater infiltration of $CD20^+$ B cells forming lymphoid follicles in fibrotic lung tissue and an improved survival compared to those with a negative autoimmune profile (30).

Genetic susceptibility

Except for the pathogenesis mentioned above, a potential genetic susceptibility may explain more why not all the smokers have CPFE. The previous study had demonstrated the differences in gene expression between fibrotic and emphysematous lesions in CPFE patients (31). In the fibrotic lesions, genes associated with the immune system were highly expressed, while genes related to the cellular fraction, membrane biology, and vascular biology were highly expressed in emphysematous lesions. The authors proposed that development of coexisting fibrotic and emphysematous lesions in CPFE was implemented by these different patterns of gene expressions. Therefore, the heterogeneity of gene expression may be associated with a potential genetic susceptibility in CPFE patients.

Plausible genetic pathways have been confirmed in several reports. In a case report, a 32-year-old female who had never smoked was identified CPFE and found having mutations in the surfactant protein C gene (32). Another case report about a 41-year-old male nonsmoker who had an *ABCA3* mutation with the typical CT findings of CPFE was published in a recent time (33). These mutations are known to cause dysfunction of surfactant homeostasis and injury or death of alveolar epithelial type II cells. In addition, both pulmonary fibrosis and COPD have been proved associated with abnormal ageing accelerated by oxidative stress and telomere shortening. Telomere length is known to be associated with familial and sporadic IIPs (34). Mutations in the essential telomerase genes (*hTERT* or *hTR*), which can cause telomere shortening, are risk factors for pulmonary fibrosis in up to one-fifth of familial cases (35). Likewise, Alder *et al.* had demonstrated that short telomeres can lower the threshold of cigarette smoke-induced damage and become a genetic susceptibility factor for emphysema, potentially contributing to its age-related onset in humans. The authors reported a case with onset of CPFE at age 34 years, who had a family history of lung diseases and all the family carrying an inherited mutation in the *hTR* (36). Recently, Nunes *et al.* also reported a family with a mutation in the *hTERT* and several individuals with emphysema or the CPFE phenotype (37). Therefore, a possible contribution of telomerase abnormalities can be considered to explain the CPFE syndrome as well.

In conclusion, the pathogenesis of CPFE is still not clear and may involve a variety of unknown cytokines and signaling pathways in the process. Overexpression of inflammatory mediators, such as *PDGF*, *TNF-α* and *TGF-β* had been proved associated with the lesions of emphysema and fibrosis (13). A recent study analyzing the BAL fluid from patients with IPF found that the concentrations of chemokine ligand 5 (*CXCL5*) and chemokine ligand 8 (*CXCL8*) were significantly higher in those with concomitant emphysema (38). These inflammatory mediators are associated with neutrophil accumulation in airspaces, which may initiate a vicious cycle of attempts at alveolar regeneration and uncontrolled activation of fibrosis proliferation through unknown pathways. In another previous study, alveolar fraction of exhaled nitric oxide in CPFE patients was found higher than that in emphysematous patients, but similar to IPF-alone patients (39). This indicated that pulmonary inflammation in CPFE was more similar to IPF and pulmonary fibrosis lesions may play a more important role in the progression of CPFE.

Clinical symptoms

Cough and dyspnea are common symptoms in patients with CPFE or COPD or IPF. However, some differences exist among them. The characteristic symptoms of COPD are chronic cough with daily variable sputum production and progressive dyspnea. Chronic cough and sputum production usually precede airflow limitation by many years (40). As for patients with IPF, dyspnea is the primary symptom existing over 90% of patients at the time of diagnosis, followed by frequent dry and nonproductive cough experienced by 73-86% of patients in the late stage (41). The symptoms of CPFE seem more similar to that of IPF. Progressive shortness of breath is the most common and classical symptom and usually more severe, especially exertional dyspnea (exists in almost all the patients; functional class III to IV of the New York Heart Association). Other common signs and symptoms of respiratory tract, such as cough, wheezing, perioral cyanosis, asthenia and so on, may also appear in some patients. On physical examination, patients with CPFE usually have inspiratory dry crackles named 'velcro sounds' from the underlying pulmonary fibrosis on chest auscultation, as reported in 87-100% of cases, and a number of them (43-45%) have finger clubbing (42).

High-resolution computed tomography (HRCT)

Currently there is no consistent definition of CPFE. HRCT scanning is essential for the diagnosis of CPFE.

The diagnostic criteria of CPFE described by Cottin *et al.* included radiological findings of upper-lobe centrilobular and/or paraseptal emphysema with multiple bullae and lower-lobe honeycombing with subpleural reticular opacities and traction bronchiectasis, and sometimes ground-glass opacities (5).

The upper-lobe emphysematous lesions in CPFE mainly include centrolobular emphysema, paraseptal emphysema and bullae, with the prevalence 97%, 93% and 54% described respectively in a study by Cottin *et al.* (42). There are differences in the distribution of emphysema between CPFE and COPD. Emphysema secondary to smoking was reported typically centrilobular in COPD. This kind of emphysema was also frequent in CPFE but no significant difference was found between two groups (P=0.067) (43). However, paraseptal emphysema was much more frequent in the CPFE group than the COPD group and was considered as the most typical presentation of CPFE (42).

Thick-walled cystic lesions (TWCLs) are considered as unique radiological and pathological features of CPFE as well (44). Enlargement of TWCLs is probably an indication of interstitial pneumonia deterioration. In a recent research, both radiological and pathological TWCLs were observed in 72.7% of the CPFE patients, but not in any patient with IPF or emphysema alone. The authors also found that the extent of emphysema was greater in the CPFE patients with TWCLs than that in the patients without TWCLs (19).

As for the lower-lobe fibrosis lesions, honeycombing, reticulation and traction bronchiectasis are the top-three common imaging features, with the prevalence of 75.6-95%, 84.4-87% and 40-69% reported in cases with CPFE (27,42). Except the abnormalities mentioned above, areas of ground glass attenuation are also common in CPFE, as reported by 62.2-66%, being the unique feature suggesting possible smoking-related ILD, such as desquamative interstitial pneumonia (12).

In the aspect of HRCT scores, the total emphysema scores were reported highest in COPD and higher in CPFE than in IPF. Besides, the total emphysema scores of CPFE were similar to that of mild to moderate COPD and lower than that of severe COPD (16). Fibrosis scores are generally higher in CPFE and IPF than that in COPD. However, the difference of fibrosis scores between CPFE and IPF was still controversial. Some reports found no difference while others showed lower total fibrosis scores in CPFE than IPF and found the difference was consistent in upper, mid and lower lung zones (15,16).

Recently there is a new report about the comparison of CPFE patients with and without airflow obstruction (CPFE OB^+ group and CPFE OB^- group) (45). The degree of emphysema represented by LAA scores on HRCT was significantly lower in the CPFE OB^- group than the CPFE OB^+ and COPD groups, while the severity of pulmonary fibrosis was greater in the CPFE OB^- group than the CPFE OB^+ group. Different mechanisms may be involved in the development of clinical phenotypes of CPFE, which might be classified into "emphysema-dominant" phenotype or "fibrosis-dominant" phenotype.

The distribution of emphysema and fibrosis in patients with CPFE are not completely independent from each other. Brillet *et al.* had described three patterns of distribution in CPFE: a progressive transition from apical emphysema to a zone of transition between bullae and honeycombing; paraseptal emphysema with areas of fibrosis; separate processes with independent areas of fibrosis and emphysema (46). Sometimes differentiating emphysema from pulmonary fibrosis may be complex and difficult. For example, wall-thickened emphysematous changes may be mistaken for honeycomb cysts. Moreover, as reported by Cottin only 50% patients with CPFE had simultaneous emphysema and pulmonary fibrosis at diagnosis; others might develop another lesion after a long history of emphysema or pulmonary fibrosis (42). So patients with suspected CPFE should be followed up on a regular basis.

The findings above reveal that CPFE is a heterogeneous disease and may have distinct phenotypes. The relative contributions of emphysema and fibrosis can vary among patients with CPFE. Diagnosis criteria of CPFE on HRCT described by Cottin *et al.* includes only upper-lobe emphysema and lower-lobe fibrosis (5), however, lacks of specific quantitative methods to assess the degree of emphysema and fibrosis, which may make the diagnosis more effective and accurate. Therefore, standard quantitative methods for diagnostic criteria in CPFE are still needed to explore and establish.

Pulmonary function tests (PFTs)

CPFE has a characteristic pulmonary function feature different from pure emphysema and IPF, which is characterized by the unexpected relatively normal lung volumes contrasted by a severely reduced diffusing capacity. In many research, mean values of forced vital capacity (FVC) and total lung capacity (TLC) in CPFE are usually

within relatively normal range, whereas DLco is severely diminished (15,27,47). The preserved lung volumes may be attributed to the counterbalanced effects of the hyperinflation defect of emphysema and the restrictive defect of pulmonary fibrosis. And the reduced diffusing capacity may be due to the overlapping negative effects of both emphysema and pulmonary fibrosis on the gas exchange (4,22,47).

For emphysema/COPD, it tends to increase lung compliance, enlarge lung volumes and residual capacity (RV) with reduced maximal expiratory flows and decreased DLco. In most research, higher forced expiratory volume in the first second (FEV_1) and FEV_1/FVC, lower RV and TLC, and lower DLco are usually observed in patients with CPFE than in patients with COPD (15,19). In one study showing annual changes of lung function between CPFE and COPD, Kitaguchi *et al.* reported that annual decreases in lung volumes (VC and FVC) and gas-exchange (DLco and DLco/VA) were significantly higher in the CPFE group than the COPD group. However, annual decrease in airflow limitation represented as FEV_1/FVC was significantly lower in the CPFE group than the COPD group (22). This may be explained by the traction caused by pulmonary fibrosis in CPFE, which prevents the typical expiratory airway collapse seen in emphysema and strengthens the support of the small airways.

For pulmonary fibrosis, it tends to decrease lung compliance and reduce TLC, RV and RV/TLC ratio with preserved or increased maximal expiratory flow rates and reduced DLCO. Generally, patients with CPFE usually have higher lung volumes, lower FEV_1/FVC ratio and lower DLco than patients with IPF (4,14). In spite of a lower baseline DLco in the CPFE group than that in the IPF group, Akagi *et al.* reported that the annual rates of decline in DLco and FVC were also significantly lower in the CPFE group (48). The existence and range level of emphysema are important factors promoting decline in the pulmonary function of IPF, such as FEV_1/FVC. In several studies showing annual changes of lung function between CPFE and IPF, the FEV_1/FVC ratio in CPFE significantly decreased during the follow-up period while that in IPF remained nearly consistent over time (21,22,48). These results suggest that CPFE is more associated with a progressively obstructive pattern over time and highlight the importance of bronchodilator therapy in CPFE.

The different pulmonary function impairment between CPFE patients with and without airflow obstruction has been recently reported (45). Impairment of diffusion capacity was severe in both CPFE OB^- and CPFE OB^+ groups. Although there were no significant differences in the dynamic hyperinflation between CPFE OB^- and CPFE OB^+ groups, lung hyperinflation and respiratory resistance were significantly lowest in CPFE OB^- group and lower in CPFE OB^+ group than the COPD group. In addition, CPFE OB^+ patients with more emphysema were also found to have a worse survival than CPFE OB^- patients.

In the end, it is worth noting that the pattern of normal lung volume with severely decreased DLco in PFTs does not necessarily mean CPFE syndrome. It may be explained by other abnormalities, such as pulmonary vascular disease, emphysema and ILD. In a report, only 16% of patients with severely diminished capacity of gas exchange had CPFE, with the remainder having emphysema (46%), ILD (28%) or PAH (8%) (7).

Blood gas analysis

Resting and exercise hypoxemia are most frequent in patients with CPFE because of the severely damaged capacity of gas exchange, whereas hypercapnia hardly appears, usually with normal average levels of $PaCO_2$ (47). Hypoxemia in the CPFE syndrome is generally moderate or above at rest and gets worse during exercise (49). In a study by Cottin *et al.* the average value of PaO_2 at rest in 61 patients with CPFE was present by 8.4±1.9 kPa while $PaCO_2$ was shown 4.9±0.7 kPa. And the prevalence of hypoxemic (PaO_2 <10 kPa) was shown in 82% of patients at rest, but elevated to 86% of the tested patients when at exercise, along with markedly decreased PaO_2 (5).

The blood gas analysis of CPFE is different from that of COPD and seems more similar with IPF. For patients with advanced COPD, gas exchange abnormalities usually result in hypoxemia and hypercapnia. The carbon dioxide retention in COPD can be explained by reduced ventilation due to severe obstruction and hyperinflation with ventilator muscle impairment (40). For patients with IPF, hypoxemia and increased alveolar-arterial oxygen difference [$P(A\text{-}a)O_2$] are more usually seen, being important symbols of IPF (20). Patients with IPF also rarely present hypercapnia because there is a restrictive pattern in these patients rather than an obstructive one.

Other diagnostic methods

Recently, He *et al.* put forward a new method of better CPFE detection by using M-mode ultrasonography (50).

The authors found that patients with CPFE had the lowest diaphragmatic motion during deep breathing, while patients with COPD had less and those with IPF had normal or near-normal result. There were no differences in diaphragmatic motion between IPF patients and healthy controls. Based on these results, the authors suggested that diaphragmatic motion measured by M-mode ultrasonography during deep breathing might be a useful approach to distinguish CPFE from COPD and IPF.

Another recent study conducted by Kokuho *et al.* aimed to explore specific biomarkers for differential diagnosis of CPFE (51). The authors found that club cell secretory protein (CC16), one of the main secretory proteins in the lung, significantly increased in patients with CPFE and can effectively differentiate CPFE from emphysema alone when combined testing with KL-6 (AUC =0.828). Serum CC16 has been proved to significantly elevate in IIP, but on the contrary, decline in smokers with COPD. Therefore, the increased level of CC16 in CPFE reflects again that pulmonary inflammation in CPFE may be more similar to pulmonary fibrosis than emphysema. Further research is required to confirm this assumption and explain the pathogenesis of this phenomenon.

Complication

Pulmonary arterial hypertension (PAH)

PAH, defined as mean pulmonary arterial pressure (mPAP) >25 mmHg, is the most important complication in COPD and IPF, which usually correlates with worse survival (52). The prevalence of PAH was reported 50% in COPD and 31-46% in advanced IPF (52,53). As for patients with CPFE, the prevalence of PAH was observed 47-90% in previous studies, which was much higher than COPD and IPF (6,52,53). In a study by Cottin *et al.* (5), the prevalence of PAH was present in 47% of CPFE patients at diagnosis, and in 55% during follow-up. In another recent research there was no difference in estimated systolic pulmonary arterial pressure (esPAP) between CPFE and IPF at diagnosis, but after 12 months the esPAP significantly increased in CPFE (20). Most CPFE patients have moderate to severe PAH whereas that in COPD or IPF alone is usually mild to moderate (53). The phenomenon may be explained by an additional/synergistic effect of hypoxic pulmonary vasoconstriction and reduced capillary beds due to the combination of pulmonary fibrosis and emphysema in CPFE (6).

PAH contributes to the functional profile of CPFE (severe dyspnea, markedly impairment of gas transfer and exercise hypoxemia) and is associated with a poor prognosis in CPFE. Higher pulmonary vascular resistance, higher HR, lower cardiac index and lower DLco are associated with a worse prognosis in CPFE-associated PAH (49). An estimated 1-year survival rate of 60% was reported in a study involving 40 CPFE patients with PAH confirmed by right heart catheterization (6). Patients with CPFE-associated PAH have poorer survival than those with IPF-associated or COPD-associated PAH. In a cohort of 110 patients with PAH, patients with CPFE had a lower median survival time than those with IPF (25 *vs.* 34 months, P<0.01) (49). In another research, the 5-year survival rate was 25% in CPFE patients with PAH compared to 75% in those without PAH and 36% in those with COPD-associated PAH (52).

Lung cancer

Emphysema and IPF have also been regarded as independent risk factors for lung cancer. The incidence of lung cancer is reported 22.4-31.3% in IPF patients and 6.8-10.8% in COPD patients (19). Therefore, CPFE, which is associated with smoking and has the features of both IPF and emphysema, may also be an independent risk factor for lung cancer. A much higher prevalence of lung cancer (35.8-46.8%) has been reported in patients with CPFE than either entity alone, with squamous cell carcinoma being the most common histologic type (54,55). The highest proportion of squamous cell carcinoma may be related to a heavy smoking history in almost all the CPFE patients, because it has been reported to be more significantly associated with tobacco smoking than adenocarcinoma (54).

Kitaguchi *et al.* had found a significantly increased prevalence of lung cancer in CPFE than in COPD (46.8% *vs.* 7.3%) (27). Another recent study also reported a higher prevalence of lung cancer in CPFE than in IPF (50% *vs.* 14.5%) (20). Inversely, the prevalence of CPFE in the lung cancer population was found higher (8.9%) than isolated pulmonary fibrosis (1.3%) (55). In another retrospective research enrolling 48 patients with CPFE matched with IPF and emphysema (1:1:2), a higher risk of lung cancer was found in the CPFE (adjusted HR, 4.62) and IPF groups (adjusted HR, 4.15) than that in the emphysema group. However, no difference in lung cancer risk was found between the CPFE and IPF group (P=0.845) (54).

Patients with CPFE and lung cancer have a much poorer prognosis than those with emphysema or IPF alone (19). The median overall survival time of patients with CPFE was 10.8 months and significantly lower than that in patients with emphysema (21.9 months; P<0.001) (55). In another research, the proportion of deaths due to lung cancer was found significantly higher in the CPFE group compared to that in the IPF group (33.3% *vs.* 12.1%; P=0.0097) (56).

The location of lung cancer is also different among CPFE, IPF and emphysema. Lung cancer of CPFE and IPF group has been reported to predominantly locate in the subpleural area while that of emphysema group occurs usually in the upper lung (54,55). The similarity of location for lung cancer in CPFE and IPF suggests that emphysema may not have an additive impact on the development of lung cancer in CPFE, and this assumption can be further used to explain why there is no significant difference in lung cancer risk between CPFE and IPF.

Acute lung injury

CPFE may increase the risk of acute lung injury after lung resection surgery or chemotherapy. In a retrospective study of 487 patients undergoing lobectomy for lung cancer, Saito *et al.* found seven out of ten post-lobectomy ARDS cases (70%) had CPFE (57). Another study reported that 20 out of 101 (19.8%) patients with CPFE and lung cancer developed acute lung injury during treatment, with the incidence of 27.3%, 20% and 16.7% during the treatment of surgery, chemotherapy and radiation (55). Moreover, the prognosis of these patients was usually poor. The mortality rate and median survival time from onset of acute lung injury were 75% and 22 days, respectively. The studies above showed the vulnerability of lung in patients with CPFE. Lower transfer factor for carbon monoxide (TLCO) and FVC values as well as a higher amount of fibrosis on HRCT have been identified as significant predictors of acute lung injury after surgery (58). Therefore, it is necessary to complete the preoperative cardiopulmonary function and HRCT examination, evaluate the surgical tolerance and closely observe in the process of surgery, chemotherapy and radiation for this special group.

Prognosis

The CPFE syndrome overall has a poor prognosis with a 5-year survival of 35-80% (5,42). The median survival of CPFE patients in reported studies ranged from 2.1 to 8.5 years (47). The major causes of death in CPFE are chronic respiratory failure, PAH, acute exacerbation and lung cancer (37). High levels of KL-6 have been demonstrated as predictors of acute exacerbations in patients with CPFE (59). Pulmonary hypertension is well known to deteriorate the prognosis of CPFE. Among these patients, high mPAP, high pulmonary vascular resistance, high heart rate and low DLco are associated with poor outcome (6).

Mortality in CPFE has been reported higher than that in emphysema. In patients without malignancy, CPFE had a more than five times higher mortality risk than emphysema, whereas in those with malignancy, an insignificant higher trend of mortality risk in CPFE was also found (43,54). However, whether CPFE has a higher or lower mortality than IPF alone is still not clear. Mejía *et al.* reported a worse survival of patients with CPFE compared to those with IPF alone (49). Nevertheless, some reports showed no significant difference in the mortality between CPFE and IPF (15). Kurashima *et al*. described a worse survival in patients with IPF and suggested that emphysema might be a protective factor in patients with CPFE (56). Similar findings were also reported by Ando *et al.* who concluded that pulmonary fibrotic lesions contribute more to the progression of CPFE than emphysema lesions (60).

The inconsistent results of comparing prognosis between CPFE and IPF, on one hand, may result from a mixing of other chronic interstitial pneumonias showing different natural history in CPFE, such as fibrotic nonspecific interstitial pneumonia and so on; on the other hand, may be due to the heterogeneous studied objects based on different enrollment criteria, complications and the distribution or extension of fibrosis and emphysema. In addition, retrospective data analysis and lead-time bias might also partially explain the inconsistent results.

Predictors of mortality for CPFE had been explored by several researches. Kishaba *et al.* reported that finger clubbing and $\%FEV_1/\%FVC$ more than 1.2 were independent predictors of mortality in CPFE (59). Mejía *et al.* showed that FVC <50% predicted and esPAP >75 mmHg at diagnosis were two most important variables associated with mortality in CPFE (49). In the research of Schmidt *et al.*, a longitudinal decline in FEV_1 over 12 months was the best predictor of mortality in CPFE, whereas composite physiologic index (CPI), which was simply calculated based on DLco% predicted, FVC and FEV_1, was more meaningful in IPF. In patients with IPF, a five point increase in CPI over 12 months predicts mortality similarly to

relative declines of 10% in FVC or 15% in DLco (61). The reason why CPI can't be a prognostic predictor for CPFE is that FEV_1 and FVC have opposite effects on the CPI.

Furthermore, it was recently proposed that paraseptal emphysema is the strongest independent factor for mortality in CPFE, especially associated with high esPAP (20). The authors supposed that pulmonary inflammation and the pro-inflammatory cytokines existed in the smoking-induced centrilobular emphysema may have antifibrotic properties and protect against the adverse effects of fibrosis lesions; while paraseptal emphysema, another phenotype of emphysema, may present another lung response to smoking, leading to severe pulmonary fibrosis. Todd *et al.* also reported that patients with pulmonary fibrosis combined with advanced centrilobular or mixed emphysema had a better prognosis than those without emphysema or with paraseptal emphysema (62). However, Cottin *et al.* made a suspicious response for his conclusion and considered that there were potential biases existed in the research (63).

Treatment

There are no specific effective treatments for the CPFE syndrome at present. It seems logical to make treatment decisions based on recommendations separately for emphysema and pulmonary fibrosis. In addition, since many studies have found that cytokines play an important role in the pathogenesis of CPFE, perhaps we can use certain cytokine antagonists or alternative therapies to prevent or treat CPFE in the different stages of the disease; though it still requires validation from further clinical research.

Smoking cessation, which is the first recommended treatment for COPD and IPF, should be encouraged for CPFE as well because it may stop the progression of disease (25,40). For those who are associated with other environmental exposures, keeping away from the exposures is the most important. In order to lessen acute exacerbations and infections, patients are suggested to accept a long-term oxygen therapy and take vaccination against influenza viruses and streptococcus pneumonia. Oxygen therapy is known as the most appropriate treatment for hypoxemia and pulmonary hypertension in CPFE. For those who have an obstructive or mixed ventilation dysfunction, the use of inhaled bronchodilators may be a common practice as those with COPD usually do. However, whether patients with CPFE can benefit from bronchodilators or not remains unknown. In addition, as mentioned earlier, pulmonary function impairment was different between CPFE patients with and without airflow obstruction. Respiratory resistance in CPFE OB^- group, which is relatively normal compared with the healthy control group, tended to be lower than that in CPFE OB^+ group (45). Consequently, efficacy of inhaled bronchodilators, such as long acting muscarinic antagonist and long acting beta-2 agonist, may be different between CPFE patients with and without airflow obstruction as well. Further studies are needed to investigate the association between efficacy of inhaled bronchodilators and airflow obstruction in CPFE patients.

Systemic corticosteroids and immunosuppressant therapy may be an option for patients with CTD-associated CPFE (44); however, no randomized double-blind trials have been conducted. On the contrary, it has been reported to result in high mortality due to infections (42). Immunosuppressive therapy may also be reasonable for patients with evidence of active inflammation, such as ground-glass opacities (47). For those who have a radiological/pathological feature of UIP, Cottin et al. recommended the use of N-acetylcysteine (1.8 g/day) in CPFE (42), but there was limited evidence for its efficacy. Triple combination therapy with N-acetylcysteine, prednisolone and azathioprine, was ever commenced in many patients with IPF based on the IFIGENIA study (64). Unfortunately, the PANTHER study which assessed the triple therapy against N-acetylcysteine or placebo alone was terminated prematurely when an interim analysis demonstrated that triple therapy increased the risk of death and hospitalization (65). Consequently, the triple therapy should not be encouraged in the CPFE patients as well.

Pirfenidone, which is the first novel agent with proven clinical efficacy in the treatment of IPF, has recently been licensed by the European authorities for treating mild to moderate IPF (66). In the ASCEND trial, pirfenidone significantly improved progression-free survival in IPF patients and slowed the decline in FVC at 52 weeks. A reduction was also revealed in all-cause mortality with pirfenidone compared with placebo (67). In a recent investigation, the majority of IPF patients, including those with cardiovascular diseases and emphysema, tolerated pirfenidone well and kept a stable course of disease on treatment. Moreover, patients who had concomitant treatment with pirfenidone and CCS/NAC were found to have worse outcomes than those with pirfenidone monotherapy (68). However, the efficacy of pirfenidone in CPFE patients is still not well known. More prospective studies are needed to make a conclusion.

Nintedanib, formerly known as BIBF 1120, is a potent intracellular inhibitor of multiple tyrosine kinases that has been developed for the treatment of IPF and types of cancers. Recently, the concurrent phase 3 trials of nintedanib versus placebo in IPF, INPULSIS-1 and INPULSIS-2, including patients with early disease (FVC >90% pred), no honeycombing and/or concomitant emphysema, report that nintedanib significantly reduces the annual decline in FVC compared with placebo and there is also a trend towards reduced death rate in nintedanib but without significant differences (69). This is the first anti-cancer agent to show benefit in IPF and may play a key role in the future management of IPF. Nevertheless, whether it is also effective in CPFE patients or not remains unknown. Further clinical trials are needed to bring us a determined answer.

Specific pulmonary hypertension therapies, such as endothelin-1 receptor antagonists, prostanoids or phosphodiesterase type 5 inhibitors, had been used for treating PAH in CPFE. But most clinical trials showed no beneficial results and found that these drugs may deteriorate hypoxemia due to vasodilation which aggravated the ventilation/perfusion mismatch (52). Therefore, no other pharmacological treatment for PAH in CPFE is recommended except for long-term oxygen treatment. For patients with advanced CPFE, lung transplantation may be the only reasonable and effective measure to improve survival (6,53).

Conclusions

Whether CPFE is just a coincidence of two smoking-related lung diseases or a distinct clinical entity related to common genetic or environmental factors remains unknown. Most researchers tend to regard it as a unique entity (5,42,47). CPFE is still a rarely recognized clinical entity which may be overlooked due to subnormal lung volumes. Respiratory physicians should be aware of its existence and take more appropriate treatments while evaluating patients with severe impaired diffusing capacities out of proportion to their total lung volumes, or with pulmonary hypertension coexisting with a mixed obstructive/restrictive lung function abnormality, especially in a current or former smoker. At last, specific clinical diagnostic and classified criteria for CPFE need to be established. Moreover, an understanding of the pathogenesis, pathophysiology and prognostic factors of the CPFE syndrome is eager to be explored in more prospective cohort studies in order to develop novel effective therapeutic strategies.

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