

Management of patients with combined pulmonary fibrosis and emphysema

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Summary

Combined pulmonary fibrosis and emphysema (CPFE) was first introduced as a distinct clinical entity to describe the coexistence of any type and grade of radiological pulmonary emphysema and the idiopathic usual interstitial pneumonia CT pattern as well as any pathologically confirmed case and has been extended to include patients with emphysema and other interstitial lung diseases (ILDs), such as nonspecific interstitial pneumonia, and connective tissue disease-ILD as well. Since no certain recommendation or guideline regarding treatment strategy for CPFE patients exists, the current therapeutic option is to follow both pulmonary fibrosis and emphysema current management approach. Smoking cessation, influenza and pneumococcal vaccination should be proposed to all patients. Bronchodilator therapy could be considered in symptomatic CPFE patients with a significant obstructive pattern component in their pulmonary function testing. Dyspneic patients with CPFE might benefit from rehabilitation programs while hypoxemic patients from supplemental oxygen. No exact data exist on treatment with specific drugs for pulmonary fibrosis or/and pulmonary hypertension. In case of acute deteriora-

tion best supportive care, extensive search for the etiologic factor and extended spectrum antimicrobials should be provided. Referral for lung transplantation should be encouraged in appropriate CPFE patients.

KEY WORDS: combined pulmonary fibrosis emphysema, pulmonary hypertension, acute exacerbation, lung transplantation.

Characteristics of CPFE

The concept of combined pulmonary fibrosis and emphysema (CPFE) was first introduced as a distinct clinical entity in 2005 to describe the coexistence of any type and grade of radiological pulmonary emphysema and the idiopathic usual interstitial pneumonia CT pattern as well as any pathologically confirmed case (1). However CPFE has been described in patients with other interstitial lung diseases (ILDs), such as fibrotic nonspecific interstitial pneumonia (NSIP), and connective tissue disease-fibrotic-ILD (CTD-fILD) as well (2). Since 2005 and with the increasingly utilization of CT of the chest in everyday clinical practice

CPFE presents severely reduced DLCO, preserved static lung volumes, severe oxygen desaturation during exercise, and high prevalence of pulmonary hypertension.

(Figure 1), a lot of information has appeared in the literature concerning CPFE including a number of reviews (3, 4), but with scarce data regarding the appropriate management of this special group of patients. Based on the existing evidence, patients with CPFE are usually older males and current or ex-smokers (1) characterized by progressive dyspnea, upper-lobe emphysema, lower-lobe fibrosis, and strong impairment of gas exchange. Diagnosis is mostly based on radiological appearance typically showing centrilobular or paraseptal emphysema in the upper lobes with reticular intralobular opacities, traction bronchiectasis and honeycombing in the lower lobes, with preserved lung volumes on plain chest radiograph as a result of two opposite conditions. Physiologically CPFE patients present severely reduced lung diffusion capacity (DLCO), preserved static lung volumes, severe impairment of gas exchange further deteriorating at exercise, and high prevalence of pulmonary hypertension (PH) that adversely influences prognosis (5, 6). Actually these are the characteristic and identifiable features of this group of patients demarcating them

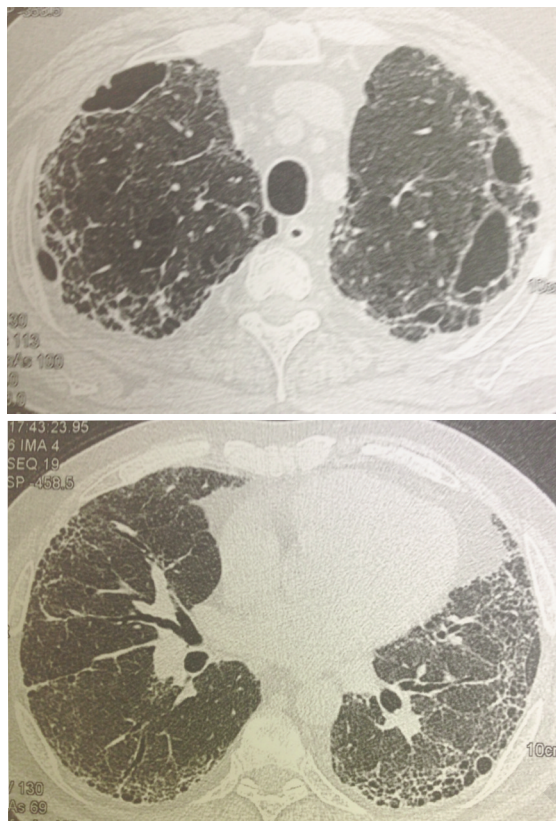


Figure 1 - Combined pulmonary fibrosis and pulmonary emphysema: characteristically emphysema is upper-lobe and fibrosis is lower-lobe predominant.

from the rest of the population of ILDs that has led to the establishment of CPFE as a distinct clinical entity. Since no certain recommendation or guideline regarding treatment strategy for CPFE patients exists, the current therapeutic option is to follow both pulmonary fibrosis and emphysema current management approach.

In most studies concerning CPFE patients the mean value of FEV₁/FVC fluctuates between 67% to 78%, with the majority of them including patients with FEV₁/FVC% above the threshold of 70% which characterizes airflow limitation in chronic obstructive pulmonary disease (COPD) (6-8). In addition, symptoms and signs indicative of a diagnosis of COPD such as progressive dyspnea, and chronic, more or less productive, cough could be also attributed to pulmonary fibrosis. Nevertheless, the component of emphysema which represents parenchymal destruction and its contribution to respiratory symptoms of CPFE patients should not be overlooked.

Are treatments for COPD and IPF useful in patients with CPFE?

Smoking cessation, influenza and pneumococcal vaccination should be proposed to all patients (9). Regarding therapy for patients in stable state, bron-

chodilator therapy with long-acting anticholinergics or beta₂-agonists is the cornerstone of COPD treatment and could be considered in symptomatic CPFE patients with a significant obstructive pattern component in their pulmonary function testing examination. The efficacy of inhaled corticosteroids is controversial in COPD patients. It has been

shown that regular treatment with inhaled corticosteroids does not modify mortality in patients with COPD (9), while they are considered to increase the risk of pneumonia (10, 11). This is a great issue for the vulnerable population of interstitial lung disease patients

Clinical trials on pirfenidone and nintedanib formally excluded patients with CPFE, so no evidence-based data support the use of these drugs for CPFE.

and therefore, inhaled corticosteroids should not be prescribed systematically in CPFE patients. Patients with CPFE can present with the clinical picture of an exacerbations of COPD, which require prompt recognition and appropriate treatment (9).

While pulmonary rehabilitation has been found to improve exercise tolerance and muscle strength, reduce the intensity of perceived dyspnea, improve quality of life and reduce the number of exacerbations for COPD patients (9), the recommendation for pulmonary rehabilitation in IPF is weak and the long-term benefit of pulmonary rehabilitation remains unclear (12-14). Dyspneic patients with CPFE might also benefit from rehabilitation programs. Patients with significant resting hypoxemia, most commonly defined as a resting SpO₂ lower than 88%, are entitled to supplemental oxygen (15).

Another significant parameter of the management of CPFE patients is consideration for lung transplantation. IPF accounts for the largest proportion of patients awaiting lung transplants and is associated with higher waiting-list and post-transplant mortality compared with other diseases (16). In a multicenter prospective cohort study a strong clinical association between higher mean pulmonary artery pressure (mPAP) and the risk of primary graft dysfunction among subjects with IPF following lung transplantation was found (17). This is of great importance in the CPFE population as PH is very common among patients of this group. Referral for lung transplantation should be encouraged in appropriate CPFE patients as it is recommended for lone-IPF patients (15).

Regarding specific treatments, IPF patients are no more treated with corticosteroids and/or other immunosuppressants (15). Moreover, there is no evidence to support the use of n-acetylcysteine and other immunomodulatory agents for IPF (15). The therapeutic strategy with the triple combination of steroids, azathioprine and n-acetylcysteine has been proved harmful for the treatment of IPF patients as shown by the interim analysis of the Panther trial that demonstrated significant increase of the risk of death, hospitalizations and exacerbations at the treated group compared to the placebo arm of the study (18). Pirfenidone, a drug with anti-fibrotic and anti-inflammato-

ry properties and a manageable tolerability profile that has been shown to slow down the progression of the disease, has been already licensed in multiple countries worldwide for the treatment of IPF, recently including Europe and the USA (19-21). In the CAPACITY trials, evidence of significant obstructive lung disease was included among exclusion criteria, despite the fact that CPFE patients were not excluded in cases of a definite diagnosis of IPF (20). In addition, in the ASCEND study, patients were excluded if they had a greater extent of emphysema than of fibrosis at the HRCT and if they had an FEV₁/FVC% ratio lower than 80% (21) and therefore it becomes obvious that a great proportion of CPFE patients have been excluded from the major trials that led to the introduction of pirfenidone as treatment of choice for IPF patients. Another agent approved simultaneously with pirfenidone by the FDA for the treatment of IPF is nintedanib, a triple tyrosine kinase inhibitor, which reduced the decline in FVC and possibly the time to the first acute exacerbations shown in two phase III trials (IMPULSIS-1, IMPULSIS-2) (22). In IMPULSIS studies patients with relevant airways obstruction and FEV₁/FVC% ratio less than 70% were excluded. Once again, it is not an unequivocal decision to treat CPFE patients with nintedanib, as trials have almost excluded this group of patients.

CPFE and co-morbidities

PH is a characteristic and common feature in the natural history of CPFE syndrome

The risk of the development of pulmonary hypertension is notably higher in patients with CPFE than in those with idiopathic pulmonary fibrosis without emphysema.

that lends clinical relevance to this group of patients as it forms a main determinant of death for them (6). All CPFE patients should undergo echocardiography for PH evaluation. Echocardiographic estimation for PH in chronic lung disease has a low positive predictive value (32%) but a high negative predictive value (93%) (23). Therefore, it is recommended that a diagnosis of PH initially diagnosed by echocardiography is confirmed by right heart catheterization (RHC). Despite the fact that occasional cases of hemodynamic or clinical improvement have been reported with specific PH therapies in CPFE, there are not randomized controlled trials to support the administration of any specific treatment (24). Furthermore, no data exist to support any specific PH treatment in IPF patients especially after the reporting of the disappointing results of recent studies (25). Further clinical trials concerning PH treatments for CPFE are needed. Another great issue for CPFE patients is the risk of developing final acute deterioration events of unknown cause, the so-called acute exacerbations of IPF (AE-IPF), in this case the development of diffuse alveolar damage upon combined usual interstitial pneumonia and emphysema, with mortality approach-

ing 100%. AE-IPF have been described in CPFE patients, although with lower rates than in lone-IPF patients in some studies (4, 26). The evidence to support treatment of AE with corticosteroids is rather weak, so best supportive care,

CPFE patients have higher risk for lung cancer than those with pure COPD.

searching for the etiologic determinant and in the meantime administration of extended spectrum antimicrobials according to the immunological status of the patient since lung infection is the most common and the most treatable triggering factor, should be the only therapeutic option (15, 27). Interestingly, corticosteroid preoperative use has been recognized as an independent risk factor for the development of an acute exacerbation of interstitial lung disease among patients with lung cancer undergoing pulmonary resection (28).

Pulmonary fibrosis is frequently associated with lung cancer, which has a significant adverse impact on survival (29, 30). Among patients with pulmonary fibrosis and lung cancer, CPFE patients are more frequently encountered compared to lone-IPF patients (30). A comparison study that evaluated the risk of lung cancer among CPFE patients compared to IPF and emphysema patients concluded that CPFE and IPF patients had a higher risk of developing lung cancer than those with emphysema, although lung cancer risk was similar between CPFE and IPF (31). CPFE patients with lung cancer show a higher risk of mortality than emphysema only patients mainly due to respiratory causes, including pneumonia (8). Moreover, the occurrence of AE for CPFE and lung cancer patients with the initiation of anti-cancer treatments was more often observed than for patients with isolated idiopathic interstitial pneumonias without emphysema (32). Indeed, pulmonary resection for patients with lung cancer and interstitial lung disease has been strongly associated with acute exacerbation at a substantially high rate leading to high associated mortality (28). Therefore, anticancer treatment and surgery for lung cancer should be performed with great caution in CPFE patients. Patients with CPFE who are in relatively good health and meet the recommended criteria should be offered the appropriate screening tests for lung cancer with annual low-dose HRCT of the chest (33).

Furthermore, IPF co-morbidities such as gastroesophageal reflux, obstructive sleep apnea syndrome, depression and cardiovascular disease should be promptly diagnosed and adequately treated (34).

Conclusions

Despite the fact that CPFE is now widely considered as a distinct clinical entity with a significant early mortality, studies on specific therapeutic option for CPFE patients are completely lacking. The several IPF treatment trials should encompass a sufficient number of CPFE patients, in order to expand the use of new therapeutic agents to this population with safety. However,

strategies against smoking would probably have the biggest impact on the natural history of this disease.

Disclosure

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