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Diagnosis and treatment of Combined Pulmonary Fibrosis and Emphysema (CPFE)

Made Agustya Darma Putra Wesnawa *

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia.

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Abstract

Combined pulmonary fibrosis and emphysema (CPFE) is a syndrome of combination pulmonary fibrosis and emphysema which is now widely found. Clinical characteristics of the CPFE are current or former heavy smoker, predominantly male, and symptom of shortness of breath on exertion. The standard diagnosis of CPFE is based on high resolution computed tomography (HRCT) with emphysema in the upper lung zone and fibrosis in the lower lung zone. The lung function profile in CPFE is different from patients with emphysema or pulmonary fibrosis alone. The lung volumes in CPFE is preserved, but there is significant reduction in lung diffusion capacity. CPFE has a poor prognosis. The presence of pulmonary hypertension in CPFE is a poor prognostic factor. Because there is no current standard treatment of CPFE, the focus of management is supportive therapy, management of complications, and management of exacerbation CPFE.

Keywords: Pulmonary Fibrosis; Emphysema; Smoking; Pulmonary Hypertension

1 Introduction

Emphysema and pulmonary fibrosis are two diseases with distinct clinical, radiology, and lung function characteristics. Pulmonary fibrosis is often associated with idiopathic pulmonary fibrosis (IPF), while emphysema is part of chronic obstructive pulmonary disease (COPD).(1) The combination of pulmonary fibrosis and emphysema was initially a rare condition but after the last 10-15 years it has been reported that these two conditions can coexist in patients and this overlapping condition is now known as the CPFE syndrome.(2) CPFE was first described by Cottin et al (3,4) in 2005 to explain the initial report of 8 patients with pulmonary fibrosis and emphysema as reported by Wiggins et al in 1990.(3,4)

Based on clinical, physiological, and radiology characteristics, CPFE is known as a different syndrome from each of pulmonary fibrosis or emphysema only.(5) Smoking is the only similarity between pulmonary fibrosis and emphysema, which as a risk factor for both diseases. The effect of smoking can induce telomere shortening which is a predisposing factor for pulmonary fibrosis and emphysema. Because they have the same etiological factor, pulmonary fibrosis and emphysema are thought to occur coincidental in the same area of the lung or cohabitate in an area where there is interaction between them. (5,6)

Pulmonary fibrosis and emphysema have opposite physiological effect. In emphysema, there is a decrease in lung elastic recoil and an increase in lung volume.(7) In pulmonary fibrosis, there is an increase in elastic recoil of the lung and a decrease in lung volume and distensibility.(8) Patients with CPFE have different lung function profiles, namely normal lung function tests or with impaired which is minimal, but there is decreased diffusing capacity and hypoxemia that worsen with activity. (2,5)

Combined pulmonary fibrosis and emphysema have a high mortality. This could be due to undiscovered mechanism and difficulty in diagnosis. It causes CPFE often not be diagnosed early, so when it is diagnosed has already in a state of

* Corresponding author: Made Agustya Darma Putra Wesnawa

severe disease and accompanied by several complications. The most common complication is pulmonary hypertension.(9)

Currently, there have been many studies evaluating the evaluation of emphysema in the course of pulmonary fibrosis. CPFE is a dangerous disease, because of its high mortality and currently no standard therapy. Better understanding of the pathophysiology of CPFE syndrome is needed to determine the CPFE endotype and phenotype so that personalized therapy can be determined. In this literature review, the etiopathogenesis, clinical characteristic, diagnosis and management of CPFE will be discussed.

2 Definition

Combined pulmonary fibrosis and emphysema is a syndrome with typical radiological features which consist of emphysema in the upper lobe and pulmonary fibrosis in the lower lobe which appear together on HRCT.(10) CPFE is recent knowing disease and associated with a worse natural history and prognosis than IPF or emphysema. (6,11)

CPFE has clinical, physiological, and radiological characteristics that are different from pulmonary fibrosis and emphysema.(12) CPFE can be one of the phenotypes of IPF.(4,13) The coexistence of CPFE has different pathophysiology and physiological characteristics, thus resulting different clinical and functional characteristics and prognosis compared to IPF or COPD alone. (14)

2.1 Epidemiology

The prevalence of CPFE is not known, current available data estimate a prevalence between 5-10% of diffuse interstitial lung disease cases. Ryerson et al (1) in 2014 reported CPFE cases in 8% of IPF patients. The majority of cases are male and over the age of 65 who are active smokers or former heavy smokers. Exposure to agricultural compounds is also a risk factor based on other research data.(12) Sangani et al (15) reported that prevalence of CPFE was 45% higher than previous studies. The delay in diagnosis CPFE can reach 20 months, due to multifactorial including advanced age, referral patterns, comorbidities, and other alternative diagnoses.(15)

2.2 Risk Factor and Pathogenesis

The pathogenesis of CPFE is still not clearly understood. Several studies suggest that CPFE occurs due to interaction of genetic predisposition and environmental exposure such as smoking in susceptible individual.(11,14) Pathogenesis of CPFE is complex which involving various cell types, inflammatory mediators and fibrogenesis. This process will cause a cycle of damage to alveoli epithelial cells which ends in a destruction of the lung parenchyma and disruption of the lung tissue remodeling process.(11)

Different mechanisms may play a role in the development of CPFE clinical phenotype, which can be classified as emphysema dominant or fibrosis dominant. It remains unclear whether emphysema and fibrosis develop independently or occur because of prior emphysema or fibrosis. There may be as yet undiscovered mechanisms involved in the signaling pathways and cytokines that cause emphysema or fibrosis after environmental exposures such as cigarette smoke.(9) There are several theories of CPFE pathogenesis such as;

2.2.1 Fibrosis develops into emphysema

It is still not known whether emphysema and fibrosis lesions occur independently or influence each other. One theory state that fibrosis, which is predominant in the basal areas of the lung, will cause traction in the upper lung, causing emphysema. Recently, many cases of emphysema are found to precede the occurrence of fibrosis, so theory about one component affecting the development of another is still questionable.(16,17)

2.2.2 Exposure to smoking and occupational exposure

Smoking can be a major risk factor for CPFE, because smoking history is a factor that is always present in all reported cohorts. (6,15) Emphysema is the lung disorder which commonly associated with smoking. Kaolinite or aluminum silicate is an industrial inorganic material found in tobacco smoke and has been isolated in alveolar macrophages of smokers with pulmonary emphysema and respiratory bronchiolitis with diffuse interstitial lung disease. Macrophage accumulation due to chronic inhalation of this mineral triggers pathological abnormalities that lead to bronchiolitis and emphysema. Smoking can induce epigenetic changes in the DNA methylation process that have been found to occur in emphysema and pulmonary fibrosis. Exposure to inorganic dust including coal dust, asbestos, and silica was also reported in case reports related to CPFE.(11)

2.2.3 Connective tissue and autoimmune diseases

Cottin et al (18) reported that the majority of patients with connective tissue disease had history of smoking and similar pulmonary function profile to CPFE. The differences were studied population was significantly younger, predominant female, and had less severe pulmonary function outcomes. (4) The most common connective tissue disease in CPFE was rheumatoid arthritis followed by systemic sclerosis and mixed connective tissue disease. Emphysema that occurs in interstitial lung disease due to systemic sclerosis is more common in non-smokers. (18,19) Ariani et al (20) showed that CPFE increases the risk of mortality in systemic sclerosis patients with reduced lung function. Therefore, patients with ILD need to be evaluated for emphysema. (20) CPFE may be associated with autoimmune disease. CPFE showed increased serum ANA results with or without positive p-ANCA titers. Early identification of CPFE patients with an autoantibody panel can provide information for effective targeted therapy.(21)

2.2.4 Genetic factors

Genetic factors that involved in lung development have an important role in the pathogenesis of lung disease. Genetic factors found to be associated with a predisposition to CPFE include polymorphisms of MMP1, MMP9, surfactant protein C(SFTPC) and TGF gene polymorphisms.(14,22) Mutations in the SFTPC gene are associated with ILD. Cottin et al (4) reported dominant mutations in the SFTPC gene in young non-smokers with CPFE and in their infants with interstitial lung disease. The pathophysiology of SFTPC-associated disease involves dysfunction of surfactant homeostasis leading to alveolar type II epithelial cell injury or death and myofibroblast proliferation. Genetically mediated alveolar injury processes may contribute to emphysema in addition to inflammation and fibrosis, and CPFE phenotype. This supports the hypothesis that patients with CPFE syndrome may have an underlying genetic predisposition.(4) Hanaoka et al investigated the genetic mechanisms of fibrotic and emphysema lesions in CPFE and found different genetic expression profiles in fibrotic and emphysema lesions. In fibrotic lesions, there is overexpression of genes related to the immune system, structural components of cytoskeleton, cell membranes, and cellular adhesions. In emphysema lesions, there is overexpression of genes related to the cellular component of membrane structure, vascular biology and growth, second messenger-mediated signaling pathways, and lung development including all processes that play a role in the destruction and repair of cells, blood vessels, and lung.(23) One of the genes that play a role in lung development is the Forkhead box protein (FoxP1-4). Andreas et al (24) shows that the protein encoded by the FoxP1 gene can have a protective effect against COPD and IPF. Disruption of FoxP1 causes increased MMP and decreased lung epithelial cell viability.

2.2.5 Aging

Early aging may contribute to the pathogenesis of COPD, IPF, and CPFE.(25,26) Recent evidence suggests that accelerating cumulative aging of the lung parenchyma plays a role in the pathogenesis of pulmonary fibrosis and emphysema either due to telomere dysfunction and genetic predisposition.(26) Telomere shortening, as a marker or aging, has been found to occur in fibrosis and emphysema.(27)The effect of smoking which induces oxidative damage can interfere with the potential regeneration of the lung precursor cell compartment, such as precursor mesenchymal cells in emphysema and alveolar epithelial precursors in pulmonary fibrosis.(25,27)

2.2.6 Inflammatory mediators and oxidative stress

Increased oxidative stress is potentially involved in the development of CPFE. Oxidative stress increases the activation of inflammatory cells which contributes to an increase in local and systemic oxidant levels. In emphysema, oxidative stress is caused by smoking resulting in cell injury and apoptosis. In pulmonary fibrosis, cellular injury occurs due to activation of fibroblasts and myofibroblasts and deposition of extracellular matrix.(14) Experimental studies in animals have demonstrated the involvement of several inflammatory mediators in the development of CPFE.(28) These inflammatory mediators can interact with environmental factors that can cause different phenotypes due to permissive genotype changes, such as;

Neutrophil elastase

Neutrophil elastase has been suggested to have a pathogenic role in the association between pulmonary fibrosis and emphysema. Neutrophil elastase regulate the expression of cytokines with mitogenic activity for mesenchymal cells that can cause emphysema and fibrosis or both.(14)

Metalloproteinases (MMPs)

MMPs are a family of enzymes produced by alveolar epithelial cells, macrophages, and neutrophils, which play a role in the pathogenesis of emphysema because they have proteolytic activity and ability to degrade collagen. Expression of MMP activity is modulated by several cytokines, including interleukin 13 (IL 13), which, in experimental models, causes

fibrosis and remodeling of airway inflammation. A recent study on CPFE patients, reported increased expression of several MMPs at sites affected by the combination of emphysema and fibrosis. This suggests that MMP has a role in extracellular matrix deposition and abnormal tissue remodeling which is a hallmark of the pulmonary fibrosis process.(6)

Platelet-derived growth factor (PDGF)

Hoyle et al (28) reported that overexpression of PDGF causes airway space enlargement, and inflammation and fibrosis in the lungs of transgenic mice. PDGF is a growth factor and has pleiotropic effects on several cell lines and involved in the pathogenesis of IPF and emphysema.(28)

Tumor necrosis factor-alpha (TNF-α)

TNF-α is a cytokine with profibrotic activity and considered as an important mediator of various pulmonary and systemic symptoms in respiratory diseases. Smoking causes release of TNF-α into the lung in both human and animal models. High level of TNF-α have been found in the sputum and peripheral blood of COPD patients.(28)

Transforming growth factor-beta (TGF-β)

TGF-β is one of the most potent profibrogenic mediators known to play a role in the pathogenesis of IPF. TGF-β1 isoform induces differentiation of fibroblasts into myofibroblasts, transition of epithelial cells to fibroblasts, and synthesis of extracellular matrix molecules, as well as promotes apoptosis of alveolar epithelial cells. Its role in the development of emphysema is unclear, although increased expression in bronchial epithelium and small airway macrophages has been observed in COPD patients.(28)

2.3 Clinical manifestations

The characteristics of CPFE patients are predominantly male (73-100%) with average age of 65-70 years and are heavy smokers or have a history of heavy smoking.(6,10) CPFE symptoms are more similar to IPF, namely progressive shortness of breath. Hypoxemia is a common finding in patients with CPFE, usually mild at rest and worsens with activity with a functional class III or IV from the New York Heart Association.(14) Other signs and symptoms reported include cough, wheezing, chest pain, perioral cyanosis, and asthenia. (1,9,12) Physical examination reveals bibasilar inspiratory crackles, wheezing, and finger clubbing. Pulmonary hypertension is a common and important complication in the natural course of CPFE, as it is associated with a worse clinical course and lower survival rates. (10,29)

2.4 Radiology imaging

Chest radiograph on CPFE shows a pattern of interstitial or reticulonodular infiltrates in the lung bases and subpleural areas, and hyperlucency at the apex with thinning of the pulmonary vessels and reduction in their number (Figure 1). The radiologic findings for fibrosis and emphysema are not well defined on chest radiographs, requiring HRCT to confirm the diagnosis. (Figure 2) Radiological criteria for determining CFPE include: (1) presence of emphysema on HRCT, defined as an area of decreased attenuation that is sharply demarcated compared to adjacent normal lung and is delimited by very thin (<1 mm) or absent walls wall, and/or multiple bullae (>1 cm) with predominance of the upper zone lung; (2) presence of diffuse parenchymal lung disease with significant pulmonary fibrosis on HRCT, defined as reticular infiltrates with a predominance of peripheral and basal, honeycomb, architectural distortion, and/or traction bronchiectasis or bronchiolectasis; focal ground-glass opacity and/or areas of alveolar condensation.(30) Emphysema lesions should be assessed as the percentage of affected lung greater than 15% for diagnosis of CPFE. (17,30)

Emphysema lesions in CPFE include centrilobular, paraseptal, and bulla emphysema. In CPFE case reports, there are many thick-walled cystic lesions (TWCL), so that it is considered as unique radiological feature of CPFE. Paraseptal emphysema is more common in CPFE than COPD. Fibrosis features of CPFE include lower lobe fibrotic, honeycombing, reticulation and traction bronchiectasis.(31)

Based on HRCT, COPD has the highest emphysema score, followed by CPFE, and IPF with the lowest score. Fibrosis scores were generally higher in CPFE and IPF than in COPD. Alsumrain et al (3) reported results of one-third of fibrosis in CPFE radiologically and clinically in accordance with IPF. Incidental findings of lung nodules or masses may occur in CPFE due to the high incidence of lung cancer in this population.

In some cases, differentiating the features of emphysema from fibrosis is difficult and complex because transitional areas can be observed between the two areas. For example, emphysematous changes or cysts around areas of ground-glass opacity can be mistaken for honeycomb cysts. Inomata et al (32) examined radiological and pathological

characteristics at autopsy of 22 CPFE patients, 8 IPF patients, and 17 emphysema patients, found thick wall cystic lesions only found in CPFE patients so that they could be considered as a characteristic of CPFE.

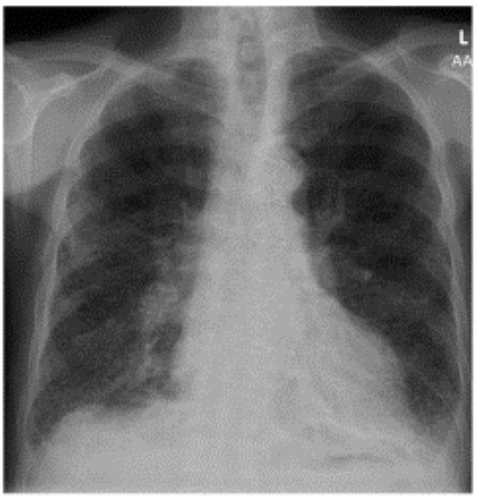

Figure 1 Chest x ray of CPFE (11)

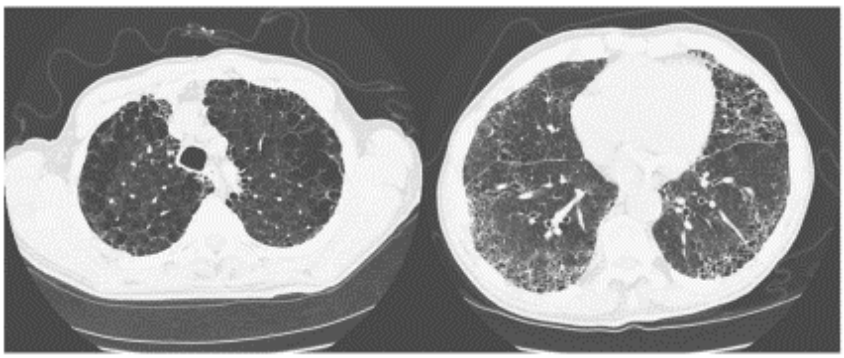

Figure 2 HRCT thorax of emphysema in upper lobe and pulmonary fibrosis in lower lobe (11)

2.5 Histopathology

Radiological findings in HRCT correlate with histopathological data. Usual interstitial pneumonia (UIP) is the most common pattern, but lesions compatible with atypical interstitial pneumonia, smoking associated ILD, or even other unclassifiable fibrotic lung disease have also been reported. Because the histopathological patterns are heterogeny, some authors recommend against using specific histopathological patterns as diagnostic criteria for CPFE.(10)

2.6 Lung function profile

The coexistence of emphysema and fibrosis lead to different characteristics of lung function with the severity of breathlessness. The lung function test in CPFE shows the forced vital capacity (FVC), forced expiratory volume in the first second (VEP1), and total lung capacity (TLC) are within the normal limit or slightly decreased.(33) The value VEP1/FVC in CPFE can be normal or slightly decreased even though there is emphysema on a HRCT scan. Relatively normal lung volumes may result from a counterbalanced effect between hyperinflation from emphysema and restriction from pulmonary fibrosis. Hyperinflation and increased lung compliance due to loss of elasticity in areas with emphysema may compensate for the volume loss caused by fibrosis.(34)

The combination of fibrosis and emphysema can cause an additive effect on lung damage, this can be seen from impaired gas exchange. On DLco examination, there was a significant decrease in diffusing capacity in CPFE patients. (2,35) A significant decrease in DLco values is caused by a decrease in the number of alveoli capillary units and the surface area for gas exchange due to a combination of fibrosis and emphysema.(2,9) This pattern of pulmonary function leads to important clinical implications. The presence of normal lung volumes does not rule out the diagnosis of pulmonary fibrosis and FVC or TLC cannot be used as parameters to monitor CPFE disease. DLco is the variable that has correlation

with the level of parenchymal damage. Low DLco values can also reflect disorders of the pulmonary vessels, especially pulmonary hypertension, because it is a frequent complication of CPFE.(9)

Measurement using the multi-frequency forced oscillation technique showed that whole breath resistance was significantly lower in patients with CPFE than in patients with pulmonary fibrosis or emphysema alone. Through M mode ultrasonography, lower diaphragm movement was obtained in patients with CPFE compared to patients with emphysema or fibrosis alone.(14) Ciftci et al (5) reported that patients with CPFE experienced decreased diffusion capacity, more severe air trapping, and muscle weakness, severe desaturation on exercise, and pulmonary hypertension.

2.7 Biomarker

Data of biomarkers in the diagnosis of CPFE still not available. However, in animal studies, an increase in inflammatory mediators was found. One of the biomarkers, club cell secretory protein (CCl6), which is the main secretory protein of the lung, found significantly increased in patients with CPFE. It can be used to differentiating CPFE from emphysema when combined with Krebs von den Lungen (KL)-6.(14,17) Examination of bronchoalveolar lavage in pulmonary fibrosis patients with emphysema found increased levels of CXC chemokines, especially CXCL5 and CXCL8. (36) Another cohort reported that KL-6, surfactant protein (SP)-D and CC16 were significantly higher in CPFE patients compared to the emphysema group. (17)

3 Complication

There are 3 complications that most often occur in CPFE such as;

3.1 Pulmonary hypertension

Pulmonary hypertension is the most common complication in the clinical course of CPFE and affecting the prognosis. The prevalence of pulmonary hypertension in CPFE varies between 47-90% and is higher than in COPD or IPF alone. (29)The diagnosis of pulmonary hypertension is determined based on a mean pulmonary arterial pressure (mPAP)>20 mm Hg via right heart catheterization.(17) The presence of pulmonary hypertension was an independent predictor of death, with a hazard ratio of 4.03. The median survival time was 6.1 years, dropping to 3.9 years in patients with CPFE with pulmonary hypertension. Routine screening for pulmonary hypertension in CPFE patients is needed through Doppler echocardiography examination. The most recent clinical classification of pulmonary hypertension by the ERS/ATS, CPFE is included in group 3 (due to pulmonary disease and/or hypoxia) under the term other pulmonary diseases with a mixed restrictive and obstructive pattern. (9)

3.2 Lung cancer

Emphysema and IPF can be considered as independent risk factors for lung cancer. CPFE is also related to smoking, which is also an independent risk factor for lung cancer. A higher prevalence of lung cancer was reported in CPFE compared to COPD or IPF. Kitaguchi reported that the prevalence of lung cancer was higher in CPFE compared to COPD.(9) The most common type of lung cancer found in CPFE was squamous cell carcinoma.(17,31) CPFE can increase the risk of acute lung injury(ALI) after lung resection surgery and chemotherapy.(14) Preoperative assessment including lung function tests and HRCT must be carried out followed by close observation during surgery, chemotherapy, and radiation in patients with CPFE.(9,11)

3.3 Acute exacerbations

CPFE patients can experience acute exacerbations of either acute exacerbation of IPF or acute exacerbation of COPD. CPFE patients with acute exacerbations of COPD have a better clinical outcome than acute exacerbations of IPF. It is necessary to investigate other conditions that may mimic CPFE exacerbations, such as infection, acute respiratory failure, pulmonary embolism or pneumothorax.(37)

4 Treatment

Currently there is no specific effective treatment for CPFE. The choice of treatment is still based on the opinion of experts regarding the therapy of emphysema and pulmonary fibrosis.(10,14) There are studies on cytokines that play a role in the pathogenesis of CPFE, so that the use of cytokine antagonists can be an alternative therapy to prevent or treat CPFE, but further research is still needed to validate its benefit.(28) Because there are no standard therapy guidelines, the principles of CPFE management are supportive therapy, which includes;

4.1 Smoking cessation

It is the main recommendation in the management of COPD and IPF because it can help prevent disease progression.(9) The smoking cessation program is the first recommendation in the management of CPFE which is useful for stopping the development of emphysema lesions.(4,38)

4.2 Vaccination

Vaccination can reduce the risk of exacerbation due to infection. CPFE patients are advised to get influenza, pneumococcal and COVID 19 vaccines. (9,17,28)

4.3 Oxygen therapy

Oxygen therapy is the most appropriate therapy for hypoxaemia and pulmonary hypertension in CPFE.(9)

4.4 Bronchodilator therapy

In CPFE patients with obstructive disorders or mixed ventilation dysfunction, the use of inhaled bronchodilators can be administered according to COPD guidelines. However, the effectiveness of bronchodilators in CPFE is still unknown. (9,28)

4.5 Corticosteroids and immunosuppressant therapy

Corticosteroid can be an option in CPFE cases associated with connective tissue disease, but there have been no clinical trials on its use in CPFE. Treatment with immunosuppressive therapy may be given to patients with evidence of active inflammation, such as ground glass infiltrates. However, this therapy is not effective in emphysema with end-stage idiopathic pulmonary fibrosis. CPFE patients with UIP features, recommended administration of N-acetylcysteine (1.8 g/day), but the evidence of its efficacy is still limited. (9)

4.6 Antifibrotic

Treatment with pirfenidone and nintedanib in IPF may have benefits for CPFE patients, but further research is needed to determine its effectiveness in preventing progression and survival. (14,28)

4.7 Therapy of pulmonary hypertension

The possibility of using approved specific therapies to treat pulmonary hypertension such as endothelin-1 receptor antagonists, prostanoid, or type 5 phosphodiesterase inhibitors, as in COPD or IPF, has been considered by several authors. However, there has been no published research regarding this issue. It is important to point out that the presence of emphysema and abnormal changes in the pulmonary vasculature could be associated with an imbalance in the ventilation/perfusion (V/Q) ratio, since hypoxic vasoconstriction is one of the main mechanisms to be avoided. These vasodilators may exacerbate hypoxemia by inhibiting this mechanism. Thus, appropriately designed trials are needed to study the effects of these drugs on gas exchange in CPFE.(9) Comprehensive evaluation is needed in patients with pulmonary hypertension, considering the cause of pulmonary disease such as CPFE.

4.8 Lung transplantation

Lung transplantation should be considered in CPFE patients because of its high mortality. Lung transplantation can be the only appropriate and effective therapy to increase survival. (9,28) Takahashi et al (39) found that after lung transplantation, CPFE patients experienced more primary graft dysfunction, acute cellular rejection, and chronic lung allograft dysfunction when compared to IPF patients. However, the 5-year survival rate is not significantly different from IPF patients. (39)

4.9 Pulmonary rehabilitation

Patients with emphysema should be included in a pulmonary rehabilitation program. The goal is to help reduce symptoms, improve exercise tolerance and better quality of life. (9,28)

4.10 Exacerbation management

The management of CPFE exacerbations follows the guidelines for the management of exacerbations of the more dominant components, namely the management of COPD exacerbations and the management of pulmonary fibrosis exacerbations.(14)

5 Prognosis

CPFE has a poor prognosis with 5-year survival of 35-80% and median survival of 2,1 to 8,5 years. The main causes of mortality in CPFE are pulmonary hypertension, chronic respiratory failure, and lung cancer. The presence of pulmonary hypertension is a predictor of mortality in patients with CPFE. If pulmonary hypertension is present, the 1-year survival is only 60%. (12) Changes in lung function in IPF are different from CPFE syndrome. Akagi et al reported that patients with CPFE experienced a slower decrease in FVC and DLco than IPF patients. Schmidt et al reported that decreased VEP1 was a predictor of mortality in CPFE patients compared to other lung function parameters. CPFE with UIP-type pulmonary fibrosis or secondary ILD has a poorer prognosis than CPFE with unclassified fibrosis. Age factor, decreased DLco and right ventricular dysfunction are predictors of mortality in CPFE. (3,40)

6 Conclusion

CPFE syndrome is a newly recognized disease which has a poor prognosis, because of its often not diagnosed early and there is no scientific evidence in its management. The relationship between emphysema and fibrosis can occur due to coincidence or cohabitation, but pathogenesis mechanism is still unknown. Smoking is a risk factor for emphysema, pulmonary fibrosis, and CPFE, each of which has differences in treatment, complications, and prognosis. It is necessary to identify the genetic and molecular biology involved in the pathogenesis of CPFE syndrome to provide a more effective approach for early diagnosis and targeted molecular therapy in the future. Further research is needed to determine the pathogenesis of CPFE through a diagnostic approach with materials from lung tissue through lung biopsies or lung surgery. Better understanding of the natural course of CPFE syndrome is needed, because these patients are different from emphysema only or fibrosis only patients, so that when given therapy according to IPF or COPD only it becomes less useful or can produce unwanted effects.

Compliance with ethical standards

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Disclosure of conflict of interest

The author declares there is no conflict of interest.

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