SAR Journal of Medicine

Abbreviated Key Title: *SAR J Med*
Home page: https://sarpublication.com/journal/sarjm/home
DOI: 10.36346/sarjm.2023.v04i01.002

ISSN 2707-773X (P)
ISSN 2709-6920 (O)

Case Report

Case Report with Review of Literature: Combined Pulmonary Fibrosis with Emphysema (CPFE)- Case Report

Shital Patil, MD FCCP[1*], Neel Tandel, MD[2], Laxman Kasture, MD[3]
[1]Associate Professor, Pulmonary Medicine, MIMSR Medical College, Latur, Maharashtra, India
[2]Junior Resident, Radiodiagnosis, MIMSR Medical College, Latur, Maharashtra, India
[3]Professor, Radiodiagnosis, MIMSR Medical College, Latur, Maharashtra, India

***Corresponding Author:** Shital Patil
Associate Professor, Pulmonary Medicine, MIMSR Medical College, Latur, Maharashtra, India

Article History: | Received: 05.01.2023 | Accepted: 11.02.2023 | Published: 15.02.2023 |

Abstract: Commonly described smoker's lung disease are emphysema, chronic bronchitis, lung cancer, and interstitial lung disease (ILD). CPFE is heterogenous lung disease documented in smokers which includes emphysema in upper lobes and pulmonary fibrosis in lower lobes. In this case report, we have reported a 80-year male presented with progressive shortness of breath with fatigability and hypoxia treated as emphysema with inhaled bronchodilators. Response to medical treatment was not satisfactory with worsening of shortness of breath and fatigability. Clinical examination revealed bilateral basal Velcro crepitation's with resting oxygen saturation was 88% at room air. High resolution computerized imaging documented emphysema in upper lobes with honeycombing and tractional bronchiectasis in lower lobes. Echocardiography documented pulmonary hypertension with dilated right atrium and ventricle. We have treated with oxygen supplementation during rest and ambulation, long-acting inhaled bronchodilator medicines and antifibrotic Nintedanib with strict counselling for avoidance of tobacco exposure. Cardiopulmonary parameters improvement including in 6-minute walk distance was significant with bronchodilators and antifibrotics.

Keywords: CPFE, Smoker's lung, Velcro Crept's, Interstitial lung disease, Nintedanib.

INTRODUCTION

Combined pulmonary fibrosis and emphysema (CPFE) is an underrecognized syndrome characterized by chronic, progressive disease with a dismal prognosis. Frequent co-morbidities with a higher incidence than in idiopathic pulmonary fibrosis or emphysema alone are pulmonary hypertension (WHO group 3) in 47–90% of the patients and lung cancer in 46.8% of the patients [1]. According to the definition of emphysema, the presence of excess fibrosis has been historically excluded from the diagnosis of emphysema [2]. 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. 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 [3]. 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)", 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 [4]. 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 [5]. 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.

CASE SUMMARY

86-year-old male, retired military professional, ex-chronic smoker, normotensive, non-diabetic, referred to our center by family physician for progressive worsened shortness of breath from grade I to grade IV over period of 2 years. He was having chronic dry cough and shown partial response to inhaled bronchodilators and inhaled corticosteroids. Family members said that he was treated with systemic steroids for recurrent and progressive respiratory symptoms with hospitalization for worsening in last 2 years. He was chronic cigarette smoker with smoking index of 50 pack years. Past hospitalization records noted chest Xray abnormalities as inhomogeneous parenchymal infiltrates (Figure 1 taken two years before) treated as COPD. Second chest Xray taken 6 months before our referral shown inhomogeneous parenchymal infiltrates with blurred cardiac and diaphragmatic margins (Figure 2).

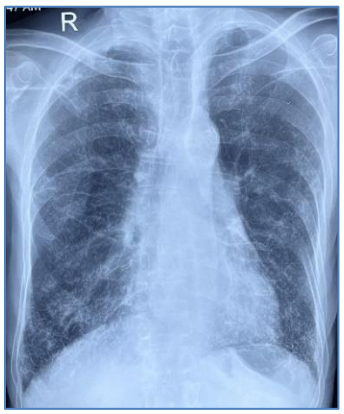

Figure 1: Chest X-ray PA view showing inhomogeneous parenchymal infiltrates

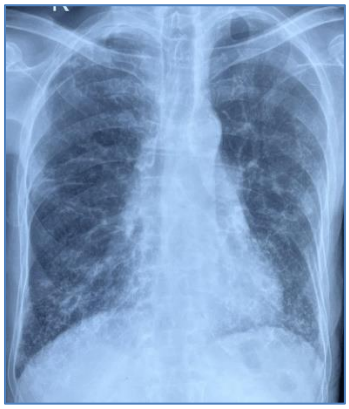

Figure 2: Chest X-ray PA view showing inhomogeneous parenchymal infiltrates with blurred cardiac and diaphragmatic margins

Clinical examination documented-
Thin built, cachexic restless male, cyanosis and clubbing present
Heart rate-118/min Respiratory rate: 30/bpm, BP-110/60 mmhg
PsO2: 72% @ room air resting & 89-96% @ with oxygen supplementation 2 liter/min by nasal canula
Respiratory system examination revealed- bilateral breath sounds normal, adventitious sounds as bilateral Velcro crepitation's heard bilateral basal area
Nervous system examination- higher functions normal, no neurological abnormality, cranial nerves normal, recent and past memory normal recall.
Cardiovascular and gastrointestinal systems were normal.
We have done HRCT thorax due to Velcro crepitation's and signs of interstitial lung disease on chest Xray. HRCT thorax documented emphysema in upper lobes and bilateral peripheral subpleural linear, reticular opacities with honeycombing and tractional bronchiectasis suggestive of usual interstitial

pneumonia pattern. (Figure 3-8) and Electrocardiogram suggestive of p-pulmonale (Figure 9).

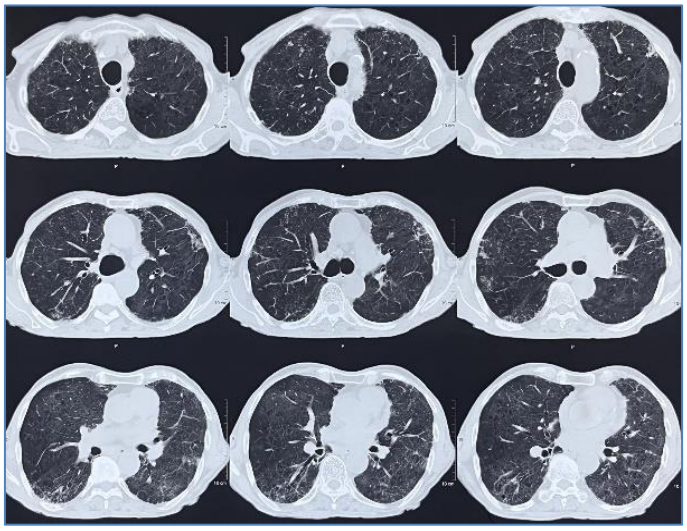

Figure 3: HRCT thorax showing bilateral peripheral subpleural interstitial reticular and linear opacities with emphysema in upper and middle lobe

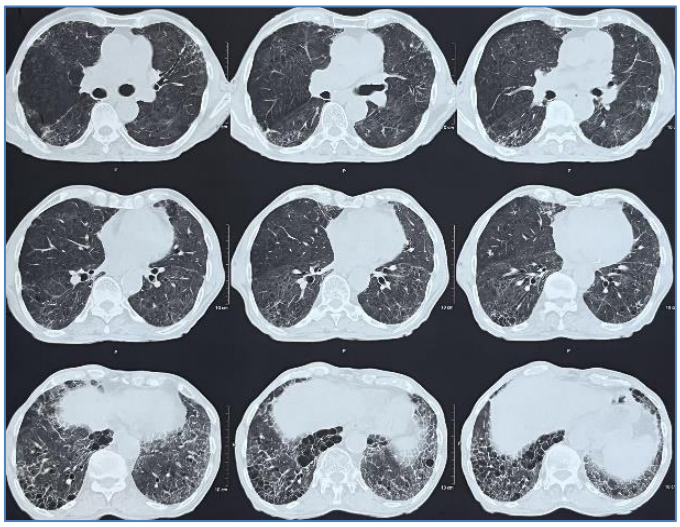

Figure 4: HRCT thorax showing bilateral peripheral subpleural interstitial linear, reticular opacites with tractional bronchiectasis and honeycombing in lower lobes

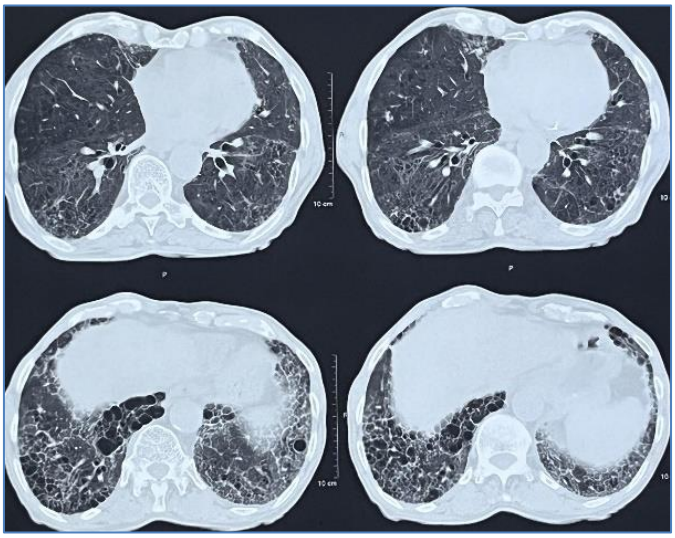

Figure 5: HRCT thorax showing bilateral peripheral subpleural tractional bronchiectasis and honeycombing

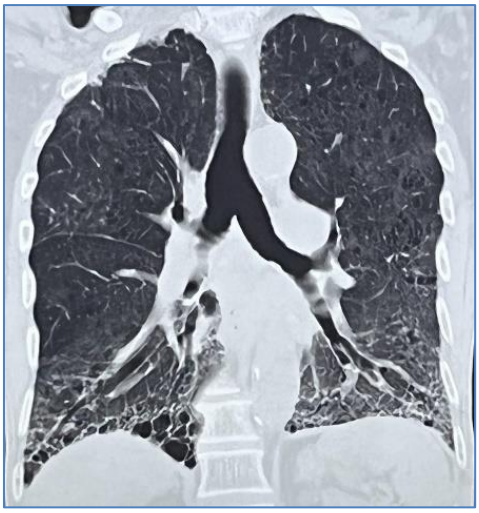

Figure 6: HRCT thorax sagittal section showing bilateral peripheral subpleural tractional bronchiectasis and honeycombing in lower lobes with emphysema

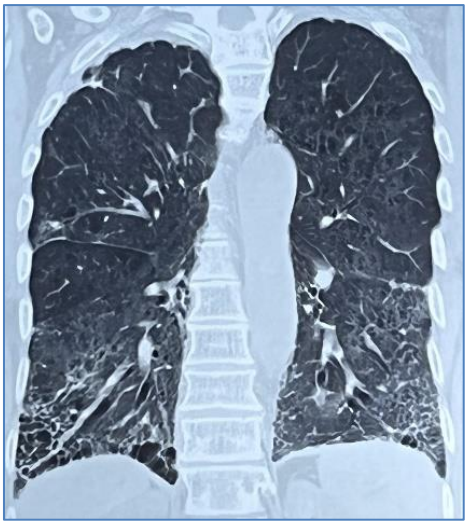

Figure 7: HRCT thorax sagittal section showing lower lobe tractional bronchiectasis and honeycombing with emphysema in upper lobes

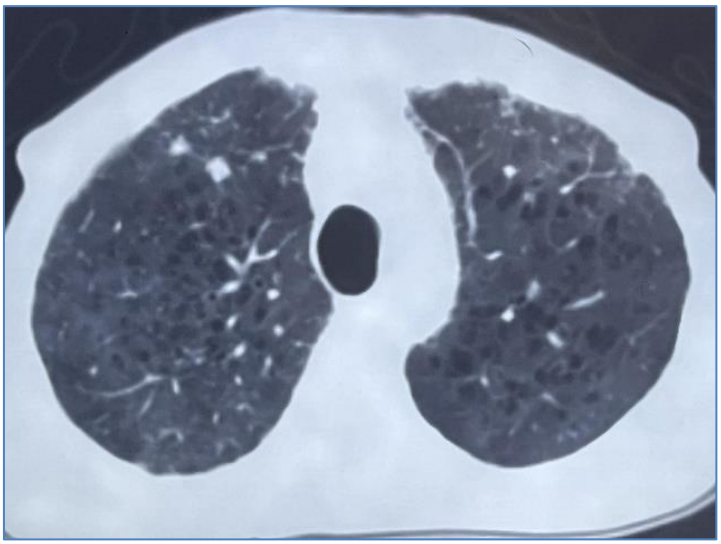

Figure 8: HRCT thorax showing interstitial opacities in bilateral upper lobes anterior aspect with bilateral upper lobe centrilobular emphysema with nodule in right upper lobe

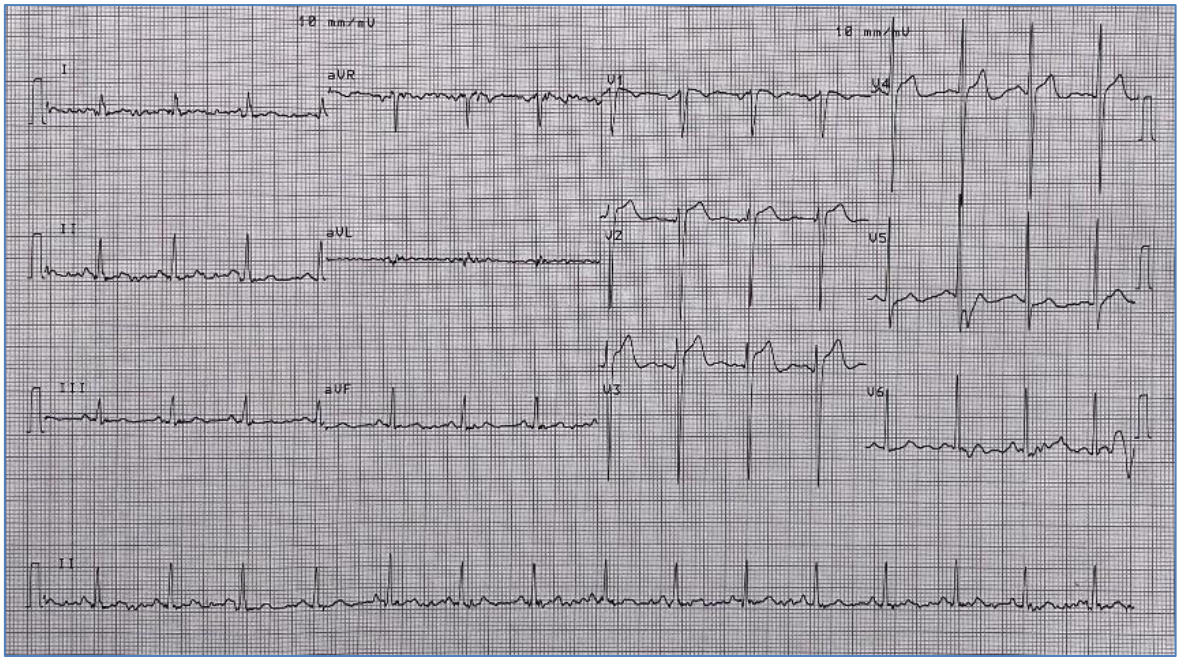

Figure 8; Electrocardiogram showing p-pulmonale in lead II and III suggestive right atrial enlargement

Laboratory examination documented as-
Hemoglobin-11.0 gm% total white blood cells-21000/mm3 Polymorphs-85%, Platelet count-490000/uL
KFT – Serum Creatinine- 1.1 mg/dl (0.6-1.2 mg/dl), blood urea- 28 mg/dl (10-40 mg/dl)
Liver function tests- Sr Bilirubin-14 mg/dl (06-1.2 mg/dl) Indriect-10.4 direct-3.6
CRP-281 mg/L (0-6 mg/L), random blood sugar level-110 mg%
LDH-1080 IU/L (70-470 IU/L), Uric acid-3.4 mg (3.5-7.5 mg/dL)
Pro-BNP- 598 pg/ml (<125 pg/ml)
Serum electrolytes: Sodium-138 meq/L (135-145 meq/L) Potassium-5.9 meq/L (3.5-5.5 meq/L) Ionic calcium-1.26 meq/L (1.09-1.36 meq/L)
D-dimer- 450 ng/ml (<500 ng/ml)
RA factor (rheumatoid arthritis)- 56 IU/ltr (0-20 IU/liter)
Anti CCP (cyclic citrullinated peptide)- <7.0 U/ml (0-17 U/ml)
ANA (anti-nuclear antibody)- negative (0-100)

Myositis profile- PL-7 positive &
OJ- Positive

Myositis panel suggestive of polymyositis in our patient as probable mechanism for CPFE other than smoking.

Spirometry analysis documented-
FVC- 50.9% (1.66 litres)
FEV1-48.1% (1.36 litres)
FEV/FVC- 105.82%

Echocardiography reported as- Evidence of severe PH RVSP by TR jet 100 mmhg, IVC dilated and noncollapsing, no evidence of clot/vegetation or embolus.

All valves normal
Dilated RA (right atrium) and RV (right ventricle)
Other chambers normal in size
Dilated main pulmonary artery
IAS and IVS intact
Normal LV function, no regional wall motion abnormality
LVEF-60%

Body plethysmography- documented
RV (residual volume)- 2.08 liter (77.2%)
TLC (total Lung capacity—4.67 liters (74.6%)
FRC- 3.20 liters (90.7%)
Suggestive of restrictive pathology.

Diffusion single breath- observed
DLCO SB- 23.3% (1.70 liters)
KCO-44.3% (0.52 liters)
VA- 40.4% (1.34 liters)
Suggestive of parenchymal restrictive disorder with diffusion abnormality.

6-MW Test- (6-minute walk test) documented
Total shuttle walk distance measured after recovery in hospitalization at time of discharge with oxygen support.
Walk distance- 150 meters with oxygen support
Oxygen saturation- 93% with oxygen support pre and 90% with increase in oxygen support post procedure (recovery time 5 minutes)
Heart rate- 96/minute pre procedure with oxygen support and 118/minute post procedure with increase in oxygen support (recovery time 5 minutes)

Reparatory rate- 26/breath per minute with oxygen support and 36/breath per minute post procedure with increase in oxygen support (recovery time 5 minutes)

PET (positron emission tomography) Scan Thorax

Imaging was done for nodular lesions in upper lobe to rule out malignancy. FDG (fluorodeoxyglucose) PET scan documented mildly FDG avid ground glassing with cystic changes and honeycombing pattern in bilateral lower lobes. HRCT imaging confirmed findings similar to FDG PET scan (Figure 9).

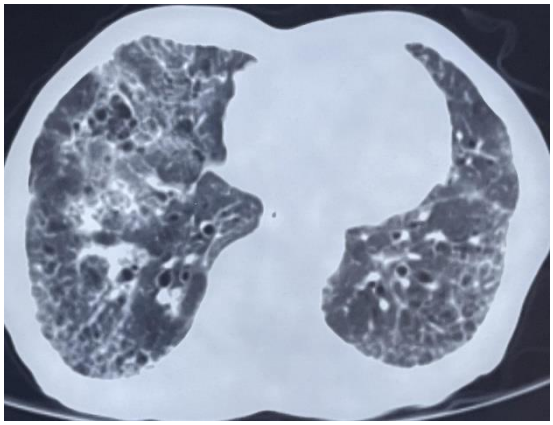

Figure 9: HRCT thorax showing honeycombing with reticular opacities in bilateral lower lobes

Treatment started with oxygen supplementation with nasal canula rate of 2 litres/minute and target oxygen saturation more than 90% during rest and increased to 4 litres during ambulation. Treatment given including injection methylprednisolone 40 mg intravenously three times, antibiotic injection meropenem 1 gram intravenous three times for exacerbation, nebulization with formoterol plus budesonide two times and Glycopyrronium one time during hospitalization, Rivaroxaban 2.5 mg as deep vein thrombosis prophylaxis, Nintedanib 100 mg two times plus Pirfenidone 400 mg three times daily for lung fibrosis, Tadalafil 20 mg one time daily for pulmonary hypertension. His health condition improved after 10 days of hospitalization and advised to continue oxygen supplementation at home during rest and ambulation. Discharged to home with Esomeprazole 40 mg one time daily, dry powder inhaler Glycopyrronium plus formoterol two times, tablet Pirfenidone plus Nintedanib, Tadalafil, Rivaroxaban and strict counselling for smoking cessation with subcutaneous injection of quadrivalent influenza and pneumococcal vaccine.

DISCUSSION

Combined pulmonary fibrosis and emphysema (CPFE) is a clinical entity characterized by the combination of upper lobe emphysema and lower lobe fibrosis. The advent of computed tomography permitted recognition of the coexistence of pulmonary fibrosis and emphysema (CPFE). 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 [6]. 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 [2]. IPF is a chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, characterized by progressive worsening of dyspnoea 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 [7].

Pathogenesis: Four Different Theories

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 signalling pathways, resulting in both emphysema and pulmonary fibrosis in genetically susceptible individuals after the exposure to environmental triggers such as smoking.

1. CPFE Starts with Fibrosis, Subsequently Resulting in Emphysema

One theory is that the fibrosis, with predominance in the basal lung parts, exerts traction on the upper parts of the lung, resulting in the development of emphysema.[4] However, emphysema most of the time precedes the fibrotic changes, which would question the appropriateness of this theory [8].

2. CPFE is Due to Gastroesophageal Reflux (GER) Promoted by Smoking Behaviour

Gastroesophageal reflux (GER) has been identified to be associated with interstitial lung diseases and is therefore considered a risk factor for the development of lung fibrosis. Smoking can increase GER and thus be responsible for development of the emphysema and indirectly (via increased GER) for the fibrotic lung changes that develop over time. This relationship is controversial and can be confounded by other effects of smoking on the lung tissue. The mechanism behind this could also be due to a sequence of events that leads first to emphysema and then additionally to fibrotic changes triggered by late-onset increased gastropharyngeal reflux. In certain individuals who are susceptible to tobacco smoke, a symptomatic smoking-related emphysema might develop. As part of standard care, a smoking cessation intervention is performed, which leads not only to smoking abstinence but also frequently to a relevant weight gain. The weight gain itself promotes increased gastropharyngeal reflux (with micro-aspirations) and thus may trigger development of fibrotic changes in the lungs. This hypothesis is compatible with the frequently observed temporal sequence of development of emphysema prior to the fibrotic changes and also with the frequently observed history (in our cohort) of strong weight gain after smoking cessation. So far, no published case series or cohort studies have systematically documented this sequence of events and the possible role of reflux and micro-aspirations in CPFE patients [9].

3. CPFE as an Autoimmune Phenomenon

A third hypothesis in a subgroup of CPFE patients could be an autoimmune phenomenon. One multicenter study investigated 40 patients with CPFE and 60 patients with IPF. A statistically significant number of CPFE patients with elevated serum ANA with or without positive p-ANCA titers were observed compared with patients with IPF without emphysema. Patients with CPFE and positive autoimmune markers showed improved survival compared to patients with a negative autoimmune profile. Moreover, a massive infiltration of clusters of CD20+ B cells forming lymphoid follicles within the fibrotic lung in CPFE patients with positive serum immunologic profile compared to patients with negative profile was noted and positively correlated with improved survival [10]. Cottin *et al*., reported a relationship between patients with connective tissue disease (CTD) and CPFE. These CTD patients had rheumatoid arthritis, systemic sclerosis, mixed or overlap CTD, or other CTDs. In this study patients with combined CTD and CPFE were significantly younger than a historical control group of patients with idiopathic CPFE and were more frequently female. In addition, patients with CTD and CPFE had higher lung volumes, lower diffusing capacity, higher pulmonary pressures, and were more frequently male than those with CTD and lung fibrosis without emphysema [11].

4. CPFE in Development Pathways Based on Genetic Factors

A genetic component may contribute to the development of CPFE. These studies are complex and so far, cannot explain CPFE development in all patients. Collum *et al*., demonstrated that both adenosine and its receptor ADORA2B are elevated in chronic lung diseases. Activation of ADORA2B leads to elevated levels of hyaluronan synthases (HAS) and thus higher concentration of hyaluronan. Hyaluronan is a glycosaminoglycan that contributes to chronic lung injury, suggesting that ADORA2B and hyaluronan contribute to CPFE [12].

Another study found an association between ABCA3 mutations and CPFE in a 41-year-old non-smoking male presenting with dyspnoea on mild exertion. The ABCA3 gene is involved in surfactant metabolism. Recessive loss-of-function mutations in ABCA3 present as lethal surfactant deficiency in the newborn, whereas other recessive mutations in ABCA3 can result in interstitial lung disease in older children [13].

Clinical symptoms:

Cough and dyspnoea 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 dyspnoea. Chronic cough and sputum production usually precede airflow limitation by many years [14]. As for patients with IPF, dyspnoea is the primary symptom existing over 90% of patients at the time of diagnosis, followed by frequent dry and non-productive cough experienced by 73-86% of patients in the late stage [15].

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 dyspnoea. 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 [16].

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

[4, 5]. The upper-lobe emphysematous lesions in CPFE mainly include centrilobular emphysema, paraseptal emphysema and bullae, with the prevalence 97%, 93% and 54% described respectively in a study by Cottin *et al*., [5]. There are differences in the distribution of emphysema between CPFE and COPD. Emphysema secondary to smoking was reported typically centrilobular in COPD. 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 [16].

Thick-walled cystic lesions (TWCLs) are considered as unique radiological and pathological features of CPFE as well [11]. Enlargement of TWCLs is probably an indication of interstitial pneumonia deterioration. In 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 [16].

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 [16, 18]. 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 [19].

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 [20]. 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 [20, 21].

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 [18, 21, 23]. 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 [23-25].

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 (FEV1) and FEV1/FVC, lower RV and TLC, and lower DLco are usually observed in patients with CPFE than in patients with COPD [17, 21]. 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) were significantly higher in the CPFE group than the COPD group. However, annual decrease in airflow limitation represented as FEV1/FVC was significantly lower in the CPFE group than the COPD group. 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 [25].

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 FEV1/FVC ratio and lower DLco than patients with IPF [3, 26]. 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 [27]. The existence and range level of emphysema are important factors promoting decline in the pulmonary function of IPF, such as FEV1/FVC. In several studies showing annual changes of lung function between CPFE and IPF, the FEV1/FVC ratio in CPFE significantly decreased during the follow-up period while that in IPF remained nearly consistent over time [25, 27, 28]. 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 [25]. 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%) [29].

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 PaCO2 [23]. Hypoxemia in the CPFE syndrome is generally moderate or above at rest and gets worse during exercise [30]. 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 [31].

Complication

1. 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 [32]. The prevalence of PAH was reported 50% in COPD and 31-46% in advanced IPF [32, 33]. As for patients with CPFE, the prevalence of PAH was observed 47-90% in previous studies, which was much higher than COPD and IPF [4, 32, 33]. In a study by Cottin *et al*., [4], 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 [34]. Most CPFE patients have moderate to severe PAH whereas that in COPD or IPF alone is usually mild to moderate [35]. 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 [5]. PAH contributes to the functional profile of CPFE (severe dyspnoea, 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 [30].

2. 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 [17]. 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. 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 [36, 37]. Kitaguchi *et al*., had found a significantly increased prevalence of lung cancer in CPFE than in COPD (46.8% vs. 7.3%) [18]. Another recent study also reported a higher prevalence of lung cancer in CPFE than in IPF (50% vs. 14.5%) [34]. Inversely, the prevalence of CPFE in the lung cancer population was found higher (8.9%) than isolated pulmonary fibrosis (1.3%) [37].

Treatment options in CPFE:

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.

1. 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. For those who are associated with other environmental exposures, keeping away from the exposures is the most important [31, 38].
2. 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. Supplemental oxygen therapy is used in the context of resting hypoxemia and may also have benefits when prescribed only for hypoxemia that occurs during exercise and nocturnally, even in those patients who are normoxemic at rest [39].
3. Regular exercise and pulmonary rehabilitation are provided to most patients with CPFE. Although no studies have evaluated pulmonary rehabilitation in CPFE, pulmonary rehabilitation and regular exercise are a cornerstone of management of patients with emphysema and are increasingly used in patients with fibrosing interstitial lung disease (fILD) [40].
4. As most exacerbations of both COPD and fILD are thought to be triggered by a respiratory tract infection (either from a virus or bacteria), influenza, pneumococcal, and

coronavirus disease (COVID-19) vaccination are also provided at standard intervals, unless contraindicated.

5. Treatment of Pulmonary Fibrosis

Decisions about pharmacologic treatment are guided by the underlying diagnosis of fILD [41]. Management of pulmonary fibrosis in the setting of CPFE is informed by the landmark clinical trials of Nintedanib and pirfenidone [42-43]. Both antifibrotic medications slow progression of mild-to-moderate IPF and other subtypes of progressive pulmonary fibrosis by approximately 50% at 12 months. Although patients with significant emphysema (greater than the volume of fibrosis on HRCT) and those with significant airflow obstruction have generally been excluded from these studies, the presence of emphysema in a proportion of patients might have contributed to slow decline in FVC in the placebo arm in CAPACITY 1 [42]. A subgroup analysis of the IPF INPULSIS trials with Nintedanib found no difference in the magnitude of the treatment effect with regard to the presence of mild-to-moderate emphysema [44]. Importantly, in the INBUILD trial of Nintedanib in fibrotic lung disease other than IPF, progressing despite management, the treatment effects were uniform across individual ILDs [45, 46]. Therefore, antifibrotic medications may have benefit in patients with IPF with CPFE, and in other forms of pulmonary fibrosis with CPFE, progressing despite management. In patients with fILD other than IPF, combined with emphysema, including fHP and CTD-ILD, glucocorticoids and/or immunosuppressive therapy may be beneficial [41].

6. Treatment of Pulmonary Emphysema

Recognition of the individual phenotype of each patient is recommended, given the lack of controlled data specific to the treatment of CPFE [47]. Inhaled bronchodilators may have benefit in select patients with CPFE who have significant airflow limitation (i.e., COPD) [48], and one uncontrolled cohort study has suggested a possible improvement in FEV1 after the use of a combination of inhaled corticosteroid and long-acting bronchodilator [39, 48]. Further studies of inhaled bronchodilators with or without corticosteroids are needed in patients with CPFE because of the relatively well-preserved spirometric values [21].

7. Treatment of Pulmonary Hypertension

Management of PH in the presence of CPFE is based on managing the underlying respiratory disorder, treating hypoxemia with supplemental oxygen, and ensuring optimal timing for lung transplant referral [5]. Controlled data do not support the use of oral PH-specific therapies, including endothelin receptor antagonists (bosentan, ambrisentan), phosphodiesterase-5 inhibitors (sildenafil, tadalafil), or stimulator of soluble guanylate cyclase (riociguat), although uncontrolled observational studies show possible benefit from PH therapies, and there are encouraging secondary endpoint trends in trials using sildenafil in IPF. Particular caution should be exercised, as treatment with ambrisentan and riociguat may be detrimental in patients with fILD and especially those with CPFE [49, 50].

In the present case report, we have documented progressively worsened shortness of breath treated as COPD with inhaled bronchodilators with corticosteroids. Clinical and radiological examination helped us to diagnose as case of CPFE in presence of bilateral Velcro Crepitations on auscultation and honeycombing in HRCT imaging. We have treated with steroids, antifibrotics, oxygen supplementation at home during rest and ambulation with pulmonary vasodilators documented satisfactory treatment outcomes as improvement in survival and quality of life.

Key learning points from this case report are:

1. Progressive shortness of breath with partial response to inhaled bronchodilator and antimuscarinic needs prompt evaluation in COPD to rule out other causes of failure of treatment.
2. Chest Xray gives definite clue for alternate diagnosis in cases with partial response to inhaled medicines in COPD.
3. Chest radiology showing blurred cardiac and diaphragmatic margins need interstitial disease to rule out. In fact, loss of demarcation of cardiac and diaphragmatic margins in chest Xray is ‘earliest marker’ of interstitial lung disease.
4. Velcro crepitations on auscultation in COPD cases is ‘clinical clue’ to suspect Idiopathic pulmonary fibrosis in cases with chronic tobacco exposure.
5. HRCT is gold standard test to evaluate interstitial lung disease. Honeycombing, tractional bronchiectasis, and reticular opacities in bilateral lower lobes with peripheral, subpleural distribution suggestive of usual interstitial pneumonia (UIP) pattern.
6. Combination of UIP pattern in lower lobes with emphysema in upper lobe is CPFE in cases with chronic smokers. With typical radiological pattern of CPFE, lung biopsy is not necessary for further confirmation.
7. Large number of CPFE cases with poor exercise tolerance (i.e., 6-minute walk distance) necessitates echocardiography to rule out pulmonary hypertension which is common but underestimated cause of persistent dyspnoea in these cases.
8. Although DLCO is decreased in both emphysema and ILD independently, it can be assessed with lung volumes. Normal lung volumes with reduced DLCO are rare in CPFE.

9. Proportionately large number of CPFE cases are having rheumatological symptoms with positive RA factor. ANA blot needs strict evaluation in all cases of CPFE to rule out concurrent CTD (connective tissue disease). Myositis and undifferentiated CTDs are common in CPFE.
10. Bronchodilators, antifibrotics with or without pulmonary vasodilators and oxygen supplementing as per oxygen saturation and echocardiography findings is mainstay therapy for CPFE.

Conflicts of Interest: Nil

Research Funding: Nil

REFERENCES

1. Hage, R., Gautschi, F., Steinack, C., & Schuurmans, M. M. (2021). Combined pulmonary fibrosis and emphysema (CPFE) clinical features and management. *International Journal of Chronic Obstructive Pulmonary Disease*, 167-177.
2. Snider, G. L., Kleinerman, J., Thurlbeck, W. M., & Bengali, Z. H. (1985). The definition of emphysema: report of a National Heart, Lung, and Blood Institute, Division of Lung Diseases workshop. *Am Rev Respir Dis*, 132, 182-185.
3. Washko, G. R., Hunninghake, G. M., Fernandez, I. E., Nishino, M., Okajima, Y., Yamashiro, T., ... & Rosas, I. O. (2011). Lung volumes and emphysema in smokers with interstitial lung abnormalities. *New England Journal of Medicine*, *364*(10), 897-906.
4. Cottin, V., Nunes, H., Brillet, P., Delaval, P., Devouassoux, G., Tillie-Leblond, I., ... & Cordier, J. F. (2005). Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *European Respiratory Journal*, *26*(4), 586-593.
5. Cottin, V., Le Pavec, J., Prévot, G., Mal, H., Humbert, M., Simonneau, G., & Cordier, J. F. (2010). Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. *European respiratory journal*, *35*(1), 105-111.
6. Grubstein, A., Bendayan, D., Schactman, I., Cohen, M., Shitrit, D., & Kramer, M. R. (2005). Concomitant upper-lobe bullous emphysema, lower-lobe interstitial fibrosis and pulmonary hypertension in heavy smokers: report of eight cases and review of the literature. *Respiratory medicine*, *99*(8), 948-954.
7. Raghu, G., Collard, H. R., Egan, J. J., Martinez, F. J., Behr, J., Brown, K. K., ... & Schunemann, H. J. (2011). An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *American journal of respiratory and critical care medicine*, *183*(6), 788-824.
8. Hiwatari, N., Shimura, S., & Takishima, T. (1993). Pulmonary emphysema followed by pulmonary fibrosis of undetermined cause. *Respiration*, *60*(6), 354-358.
9. Méthot, D. B., Leblanc, É., & Lacasse, Y. (2019). Meta-analysis of gastroesophageal reflux disease and idiopathic pulmonary fibrosis. *Chest*, *155*(1), 33-43.
10. Tzouvelekis, A., Zacharis, G., Oikonomou, A., Mikroulis, D., Margaritopoulos, G., Koutsopoulos, A., ... & Bouros, D. (2013). Increased incidence of autoimmune markers in patients with combined pulmonary fibrosis and emphysema. *BMC Pulmonary Medicine*, *13*, 1-11.
11. Cottin, V., Nunes, H., Mouthon, L., Gamondes, D., Lazor, R., Hachulla, E., ... & Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires. (2011). Combined pulmonary fibrosis and emphysema syndrome in connective tissue disease. *Arthritis & Rheumatism*, *63*(1), 295-304.
12. Collum, S. D., Molina, J. G., Hanmandlu, A., Bi, W., Pedroza, M., Mertens, T. C., ... & Karmouty-Quintana, H. (2019). Adenosine and hyaluronan promote lung fibrosis and pulmonary hypertension in combined pulmonary fibrosis and emphysema. *Disease models & mechanisms*, *12*(5), dmm038711.
13. Epaud, R., Delestrain, C., Louha, M., Simon, S., Fanen, P., & Tazi, A. (2014). Combined pulmonary fibrosis and emphysema syndrome associated with ABCA3 mutations. *European Respiratory Journal*, *43*(2), 638-641.
14. Price, D. B., Baker, C. L., Zou, K. H., Higgins, V. S., Bailey, J. T., & Pike, J. S. (2014). Real-world characterization and differentiation of the Global Initiative for Chronic Obstructive Lung Disease strategy classification. *International journal of chronic obstructive pulmonary disease*, 551-561.
15. Lee, A. S., Mira-Avendano, I., Ryu, J. H., & Daniels, C. E. (2014). The burden of idiopathic pulmonary fibrosis: an unmet public health need. *Respiratory medicine*, *108*(7), 955-967.
16. Cottin, V. (2013). The impact of emphysema in pulmonary fibrosis. *European Respiratory Review*, *22*(128), 153-157.
17. Inomata, M., Ikushima, S., Awano, N., Kondoh, K., Satake, K., Masuo, M., ... & Takemura, T. (2014). An autopsy study of combined pulmonary fibrosis and emphysema: correlations among clinical, radiological, and pathological features. *BMC pulmonary medicine*, *14*(1), 1-13.
18. Kitaguchi, Y., Fujimoto, K., Hanaoka, M., Kawakami, S., Honda, T., & Kubo, K. (2010). Clinical characteristics of combined pulmonary fibrosis and emphysema. *Respirology*, *15*(2), 265-271.
19. Nair, A., & Hansell, D. M. (2014, February). High-resolution computed tomography features of smoking-related interstitial lung disease.

In *Seminars in Ultrasound, CT and MRI* (Vol. 35, No. 1, pp. 59-71). WB Saunders.

20. Mori, K., Shirai, T., Mikamo, M., Shishido, Y., Akita, T., Morita, S., ... & Chida, K. (2013). Respiratory mechanics measured by forced oscillation technique in combined pulmonary fibrosis and emphysema. *Respiratory Physiology & Neurobiology*, *185*(2), 235-240.
21. Ryerson, C. J., Hartman, T., Elicker, B. M., Ley, B., Lee, J. S., Abbritti, M., ... & Collard, H. R. (2013). Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. *Chest*, *144*(1), 234-240.
22. Brillet, P. Y., Cottin, V., Letoumelin, P., Landino, F., Brauner, W., Valeyre, D., ... & Nunes, H. (2009). Syndrome emphysème des sommets et fibrose pulmonaire des bases combinés (syndrome emphysème/fibrose): aspects tomodensitométriques et fonctionnels. *Journal de Radiologie*, *90*(1), 43-51.
23. Jankowich, M. D., & Rounds, S. I. (2012). Combined pulmonary fibrosis and emphysema syndrome: a review. *Chest*, *141*(1), 222-231.
24. Washko, G. R., Hunninghake, G. M., Fernandez, I. E., Nishino, M., Okajima, Y., Yamashiro, T., ... & Rosas, I. O. (2011). Lung volumes and emphysema in smokers with interstitial lung abnormalities. *New England Journal of Medicine*, *364*(10), 897-906.
25. Kitaguchi, Y., Fujimoto, K., Hayashi, R., Hanaoka, M., Honda, T., & Kubo, K. (2013). Annual changes in pulmonary function in combined pulmonary fibrosis and emphysema: over a 5-year follow-up. *Respiratory medicine*, *107*(12), 1986-1992.
26. Ye, Q., Huang, K., Ding, Y., Lou, B., Hou, Z., Dai, H., & Wang, C. (2014). Cigarette smoking contributes to idiopathic pulmonary fibrosis associated with emphysema. *Chinese medical journal*, *127*(03), 469-474.
27. Akagi, T., Matsumoto, T., Harada, T., Tanaka, M., Kuraki, T., Fujita, M., & Watanabe, K. (2009). Coexistent emphysema delays the decrease of vital capacity in idiopathic pulmonary fibrosis. *Respiratory medicine*, *103*(8), 1209-1215.
28. Kim, Y. J., Shin, S. H., Park, J. W., Kyung, S. Y., Kang, S. M., Lee, S. P., ... & Jeong, S. H. (2014). Annual change in pulmonary function and clinical characteristics of combined pulmonary fibrosis and emphysema and idiopathic pulmonary fibrosis: over a 3-year follow-up. *Tuberculosis and respiratory diseases*, *77*(1), 18-23.
29. Kiakouama, L., Cottin, V., Glerant, J. C., Bayle, J. Y., Mornex, J. F., & Cordier, J. F. (2011). Conditions associated with severe carbon monoxide diffusion coefficient reduction. *Respiratory medicine*, *105*(8), 1248-1256.
30. Mejía, M., Carrillo, G., Rojas-Serrano, J., Estrada, A., Suárez, T., Alonso, D., ... & Selman, M. (2009). Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. *Chest*, *136*(1), 10-15.
31. Price, D. B., Baker, C. L., Zou, K. H., Higgins, V. S., Bailey, J. T., & Pike, J. S. (2014). Real-world characterization and differentiation of the Global Initiative for Chronic Obstructive Lung Disease strategy classification. *International journal of chronic obstructive pulmonary disease*, 9, 551-561.
32. Seeger, W., Adir, Y., Barberà, J. A., Champion, H., Coghlan, J. G., Cottin, V., ... & Vachiery, J. L. (2013). Pulmonary hypertension in chronic lung diseases. *Journal of the American College of Cardiology*, *62*(25S), D109-D116.
33. Caminati, A., Cassandro, R., & Harari, S. (2013). Pulmonary hypertension in chronic interstitial lung diseases. *European Respiratory Review*, *22*(129), 292-301.
34. Sugino, K., Ishida, F., Kikuchi, N., Hirota, N., Sano, G., Sato, K., ... & Homma, S. (2014). Comparison of clinical characteristics and prognostic factors of combined pulmonary fibrosis and emphysema versus idiopathic pulmonary fibrosis alone. *Respirology*, *19*(2), 239-245.
35. Caminati, A., Cassandro, R., & Harari, S. (2013). Pulmonary hypertension in chronic interstitial lung diseases. *European Respiratory Review*, *22*(129), 292-301.
36. Kwak, N., Park, C. M., Lee, J., Park, Y. S., Lee, S. M., Yim, J. J., ... & Lee, C. H. (2014). Lung cancer risk among patients with combined pulmonary fibrosis and emphysema. *Respiratory medicine*, *108*(3), 524-530.
37. Usui, K., Tanai, C., Tanaka, Y., Noda, H., & Ishihara, T. (2011). The prevalence of pulmonary fibrosis combined with emphysema in patients with lung cancer. *Respirology*, *16*(2), 326-331.
38. Morse, D., & Rosas, I. O. (2014). Tobacco Smoke–Induced Lung Fibrosis and Emphysema. *Annual review of physiology*, *76*, 493-513.
39. Zhang, L., Zhang, C., Dong, F., Song, Q., Chi, F., Liu, L., ... & Che, C. (2016). Combined pulmonary fibrosis and emphysema: a retrospective analysis of clinical characteristics, treatment and prognosis. *BMC Pulmonary Medicine*, *16*(1), 1-8.
40. Tomioka, H., Mamesaya, N., Yamashita, S., Kida, Y., Kaneko, M., & Sakai, H. (2016). Combined pulmonary fibrosis and emphysema: effect of pulmonary rehabilitation in comparison with chronic obstructive pulmonary disease. *BMJ open respiratory research*, *3*(1), e000099.
41. Wijsenbeek, M., & Cottin, V. (2020). Spectrum of fibrotic lung diseases. *New England Journal of Medicine*, *383*(10), 958-968.
42. Noble, P. W., Albera, C., Bradford, W. Z., Costabel, U., Glassberg, M. K., Kardatzke, D., ... & Du Bois, R. M. (2011). Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *The Lancet*, *377*(9779), 1760-1769.

43. Maher, T. M., Corte, T. J., Fischer, A., Kreuter, M., Lederer, D. J., Molina-Molina, M., ... & Cottin, V. (2020). Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. *The lancet Respiratory medicine*, *8*(2), 147-157.
44. Cottin, V., Azuma, A., Raghu, G., Stansen, W., Stowasser, S., Schlenker-Herceg, R., & Kolb, M. (2019). Therapeutic effects of nintedanib are not influenced by emphysema in the INPULSIS trials. *European Respiratory Journal*, *53*(4), 1801655.
45. Flaherty, K. R., Wells, A. U., Cottin, V., Devaraj, A., Walsh, S. L., Inoue, Y., ... & Brown, K. K. (2019). Nintedanib in progressive fibrosing interstitial lung diseases. *New England Journal of Medicine*, *381*(18), 1718-1727.
46. Wells, A. U., Flaherty, K. R., Brown, K. K., Inoue, Y., Devaraj, A., Richeldi, L., ... & Takaya, H. (2020). Nintedanib in patients with progressive fibrosing interstitial lung diseases—subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *The lancet Respiratory medicine*, *8*(5), 453-460.
47. Sato, S., Tanino, Y., Misa, K., Fukuhara, N., Nikaido, T., Uematsu, M., ... & Munakata, M. (2016). Identification of clinical phenotypes in idiopathic interstitial pneumonia with pulmonary emphysema. *Internal Medicine*, *55*(12), 1529-1535.
48. Dong, F., Zhang, Y., Chi, F., Song, Q., Zhang, L., Wang, Y., & Che, C. (2015). Clinical efficacy and safety of ICS/LABA in patients with combined idiopathic pulmonary fibrosis and emphysema. *International Journal of Clinical and Experimental Medicine*, *8*(6), 8617-8625.
49. Hoeper, M. M., Behr, J., Held, M., Grunig, E., Vizza, C. D., Vonk-Noordegraaf, A., ... & Gibbs, J. S. R. (2015). Pulmonary hypertension in patients with chronic fibrosing idiopathic interstitial pneumonias. *PloS one*, *10*(12), e0141911.
50. Behr, J., Prasse, A., Kreuter, M., Johow, J., Rabe, K. F., Bonella, F., ... & Froehling, K. P. (2021). Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *The Lancet Respiratory Medicine*, *9*(5), 476-486.