

## Case Report

### CPFE Syndrome: A Case Report

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#### Abstract:

Combined pulmonary fibrosis and emphysema syndrome (CPFE syndrome) is the co-existence of emphysema and pulmonary fibrosis. The syndrome was first described by Cottin et al., in 2005 and is characterised by upper lobe emphysema and lower lobe interstitial fibrosis. Patients with CPFE show severe dyspnoea and hypoxemia with exercise. Lung function tests (LFT) reveal a mixed pattern with relatively preserved lung volumes and severely low diffusing capacity for carbon monoxide (DLCO). CPFE is prevalent in heavy male smokers and have a high probability of developing pulmonary hypertension, acute lung injury and lung cancer.

#### Introduction

CPFE syndrome is the rare and emerging combination of emphysema and pulmonary fibrosis. Males with a history of heavy smoking are thought to be predisposed to the disease. High resolution CT (HRCT) scanning has increased clinical recognition with the simultaneous occurrence of emphysema in the upper lung zones and pulmonary fibrosis in the lower zones.<sup>1</sup> This condition is associated with significant mortality, particularly if pulmonary hypertension is present and thus, early recognition and treatment is essential.<sup>1-2</sup>

#### Case report

A 74-year-old Caucasian male was referred to respiratory outpatient clinic following a recent CT chest scan and reduced exercise tolerance with a history of chronic smoking.

He reports increasing shortness of breath, particularly when walking up a steep hill. He affirms he is able to walk one kilometre without any breathlessness, but admits to walking at a slower pace than previously. He states that he is otherwise well, and denies any chest pain, weight loss, night sweats, haemoptysis, chest pain or cough with expectoration. He has no history of asthma, orthopnoea or paroxysmal nocturnal dyspnoea.

His background history includes prostate cancer that was treated with total prostatectomy in November 2015 and radiotherapy completed in February 2017. He has a past history of diverticulosis detected incidentally on routine colonoscopy but has never had an episode of acute diverticulitis.

His medications include Spiriva Respimat two puffs mane, denosumab six-monthly and vitamin D and calcium supplements daily. He has no known allergies.

He worked in the timber industry for nine years and confirms inhalation exposure from sanding as he rarely wore personal protective equipment. He has been working as a painter and handy-man for the past 25 years. He is an ex-smoker with a 45 pack year history of smoking tobacco and with filters and ceased approximately 15 years ago. He drinks three standard drinks a day.

He has a strong family history of bowel cancer, with his father dying at 70 years old and brother dying at 83 years old of bowel cancer.

On examination, he was afebrile with a pulse rate of 80, blood pressure of 150/84mmHg, saturating at 96% on room air. He displayed no finger clubbing and on chest auscultation, there was characteristic leathery crackles at the bases as well as in the infra-axillary regions. His heart sounds were dual with no murmur and JVP was not elevated. His abdomen was soft and non-tender. His calves were soft, non-tender and there was no pitting oedema.

His HRCT scan showed bullous and paraseptal emphysema in the upper part of the lung along with some interstitial shadowing and honeycombing in the lower lobe of the lung. These CT changes were most consistent with a CPFE syndrome and further tests were conducted. His autoimmune and vasculitic screening were negative. His LFT's showed a mixed pattern of obstruction and restriction, with an FEV1 of 2.17L (82.8% of predicted), FVC of 3.25L (98.5% of predicted), FEV1/FVC ratio of 66.98 and TLC of 4.96 (76.3%). His corrected diffusion capacity was 49.2% which is moderately reduced. His echocardiogram showed mild pulmonary hypertension, with an estimated RSVF of 38mmHg. His total distance on the six-minute walk test was 380m, with his lowest SpO2 at 88% and highest HR at 100.

The patient was referred for discussion at the lung fibrosis multi-disciplinary team meeting for possibly using anti-fibrinolytic drugs and will be reviewed in reviewed in the respiratory outpatient clinic

#### Discussion

Emphysema and pulmonary fibrosis have historically been regarded as separate medical conditions, with different pathological, radiological and prognostic features. Emphysema is an obstructive lung disease most commonly caused by inhaled irritants such as tobacco smoke and air pollution.<sup>3</sup> These noxious stimuli destroy the alveoli and form large air pockets known as bullae. This results in reduced lung elastic recoil, reduced lung compliance and reduced lung volumes.<sup>4</sup> On CT, emphysema commonly manifests as patchy

centrilobular emphysematous spaced, up to 1cm in diameter, in the upper zones of the lungs.<sup>5</sup>

Pulmonary fibrosis is a restrictive lung disease where dense fibrous connective tissue replaces the lung parenchyma. This leads to the stiffening of the lungs and reduces oxygen transfer between the alveoli and alveolar capillaries.<sup>6-7</sup> In many cases, the aetiology of pulmonary fibrosis is unknown, and as such is referred to as idiopathic pulmonary fibrosis (IPF). Two common types of IPF include usual interstitial pneumonia (UIP), characterised by basal ground-glass opacities with traction bronchiectasis, and non-specific interstitial pneumonia (NSIP), characterised by patchy peripheral reticular opacities and honeycombing.<sup>8</sup> Pulmonary fibrosis may also be secondary to autoimmune disorders such as rheumatoid arthritis, inhalation of occupational pollutants such as asbestosis and silicosis or infections.<sup>6</sup>

CPFE is the co-existence of emphysema and pulmonary fibrosis in individuals.<sup>1</sup> This association was first described by Wiggen's et al in 1990 who found similarities between eight heavy smokers with severe breathlessness. He documented that all patients had radiological signs of emphysema and fibrosis on HRCT scans as well as preserved lung volumes and severely low DLCO on LFTs.<sup>9</sup> In 2005, Cottin et al conducted a retrospective study of 61 patients with combined emphysema and fibrosis and defined the syndrome as CPFE.<sup>10</sup>

CPFE characteristically presents in older male population, often after the sixth decade of life.<sup>9-10</sup> It is prevalent in patients with a heavy smoking history, usually greater than 40 pack years as noted in the case study.<sup>10-11</sup> The exact mechanism of pathogenesis is not yet fully understood and it is not yet clear if CPFE is simply a co-existence of separate medical entities or the result of a common mechanism. However, it has been suggested that CPFE is the result of the combination between genetic predisposition and environmental triggers such as smoking in predisposed individuals.<sup>1,12</sup>

Patients usually present with exertional dyspnoea, often associated with a desaturation during exercise as described by the patient. These patients may present with other clinical features involving the respiratory system including cough, sputum production, wheezing, and chest pain may also appear in some patients. Physical examination often reveals finger clubbing and basal crackles and less commonly wheezing and perioral cyanosis.<sup>10,13</sup>

As demonstrated in the case study, LFT's often reveal an overlapping restrictive and obstructive pattern with unexpected subnormal lung volumes.<sup>9-10,14</sup> The relatively normal lung volumes seen in CPFE results from the counterbalance between the hyperinflation of emphysema and restrictive effects of pulmonary fibrosis.<sup>15</sup> Often patients have a severe decrease in DLCO due to reduced vascular surface area caused by both emphysema and fibrosis.<sup>15</sup>

The diagnosis of CPFE is based on HRCT imaging.<sup>10</sup> Characteristically, HRCT shows centrilobular and/or paraseptal emphysema in the upper zones and pulmonary fibrosis in the lower zones.<sup>16</sup> The pattern of fibrosis is specific to the type of pulmonary fibrosis, however it is commonly characterised by honeycombing in the lower zones as shown in the case study. Traction bronchiectasis, reticulation, large thick-walled cystic lesions (diameter >1cm), centrilobular nodules and ground glass opacities can sometimes also be seen on HRCT.<sup>1</sup> Findings suggestive of pulmonary hypertension, such as dilation of central pulmonary arteries, right heart

enlargement and mosaic appearance of pulmonary parenchyma may be seen in severe cases.<sup>17</sup>

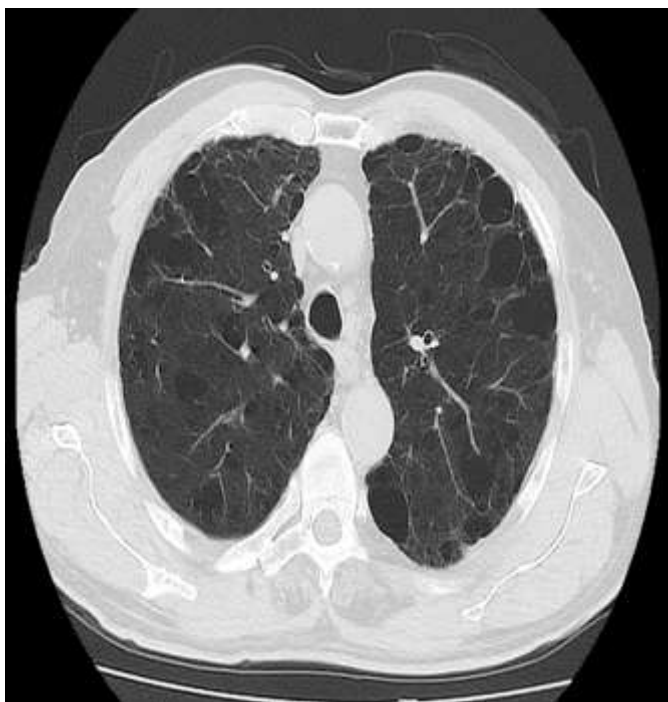
CPFE is often complicated by the development of or predisposition to developing severe pulmonary hypertension, acute lung injury and less frequently lung cancer.<sup>2</sup> The risk of pulmonary hypertension is higher than patients with only emphysema or pulmonary fibrosis due to the cumulative effect of two separate disease processes.<sup>2,18</sup> Although tobacco smoking is the largest independent risk factor for lung cancer, the chronic inflammation and repeated lung injury from emphysema and fibrosis are thought to also independently contribute to the development of lung cancer.<sup>19</sup>

The median survival of patients with CPFE has been reported between 2.1 and 8.5 years, with the 5-year survival rate between 38% - 55%.<sup>10-11</sup> FEV1 is the best predictor of mortality, with an increased rate of worsening FEV1 linked to increased mortality.<sup>20</sup> Furthermore, CPFE progresses more rapidly with active smokers compared to those who quit and therefore smoking cessation should be a constant point of discussion in each consultation.<sup>21</sup>

In regards to treatment, there are currently no exclusive recommendations available for the management of patients with CPFE syndrome. Discussion regarding smoking cessation should be re-enforced in every visit and oxygen therapy should be offered for patients with respiratory failures.<sup>21</sup> Vaccinations for influenza and *Streptococcus pneumoniae* are recommended to prevent deterioration.<sup>1</sup> Patients with airflow obstruction may benefit from inhaled bronchodilators as seen with patient in this case study.<sup>11</sup> For those patients with pulmonary hypertension, specific therapy such as endothelin-1 receptor antagonists, prostanoids or phosphodiesterase type 5 inhibitors may be discussed to improve hemodynamic functions.<sup>22</sup> Anti-fibrinolytic treatment, such as pirfenidone might be beneficial for patients and should be discussed in multi-disciplinary meetings as demonstrated in the case report.<sup>23-24</sup> Finally, patients with severe disease should also be considered for lung transplantation.<sup>15</sup>



Figure 1: Chest x-ray



**Figure 2: HRCT Upper lobe bullous and paraseptal emphysema**



**Figure 3: HRCT Lower lobe sub-pleural interstitial changes with honeycombing**

### Conclusion

CPFE is an important respiratory disorder that has an incompletely described pathophysiology with a high mortality and morbidity. CPFE syndrome should be suspected in patients with a significant smoking history with interstitial lung disease with reduced DLCO and preserved lung volumes. Early recognition, diagnosis with HRCT and treatment is pivotal to providing best patient care. However, further research is essential for increasing the understanding of the pathogenies to develop new effective treatment.

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