CASE REPORT

Deterioration of Respiratory Symptoms in Uncontrolled CPFE: A Case Report

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) has a global impact on health and increases healthcare costs. Combined pulmonary fibrosis and emphysema (CPFE) combines interstitial lung disease (ILD) and emphysema. Excessive short-acting β2-agonist (SABA) usage escalates exacerbation risk, affecting prognosis.
Case: A 44-year-old former smoker presented with worsening shortness of breath, cough, and weight loss. Examination showed respiratory distress, including wheezing. Initially, he was diagnosed with tuberculosis (TB) and COPD exacerbation. He regularly used jet nebulizers without medical supervision, and during the initial treatment, he developed acute respiratory failure, leading to acidosis. Treatment involved SABA and short-acting muscarinic-antagonist (SAMA), steroids, and oxygen therapy. In November 2023, his condition worsened, requiring emergency treatment. Radiological findings indicated CPFE. Management included nebulized medications, intravenous steroids, and antibiotics. Despite challenges, he rarely attended follow-up appointments after showing improvement, missing scheduled rehabilitation therapy, inhaler monitoring, comorbid therapy, and home oxygen monitoring.
Conclusion: Combined pulmonary fibrosis and emphysema combines ILD and emphysema, causing severe respiratory impairment. Management mirrors that of COPD, involving inhalers, corticosteroids, and oxygen therapy.

INTRODUCTION

Emphysema can occur with pulmonary fibrosis in interstitial lung disease (ILD) or combined pulmonary fibrosis and emphysema (CPFE).[1] This condition was introduced by Cottin in 2005, with respiratory symptoms that differ from typical fibrotic diseases. In CPFE, worsening respiratory symptoms are marked by declining lung function and high mortality rates.[2] Cottin diagnosed CPFE based on high-resolution computed tomography (HRCT), where a basilar usual interstitial pneumonia (UIP) pattern was observed with predominant emphysematous changes in the upper lobe (centrilobular and/or paraseptal).[3]

Patients with CPFE commonly experience activity-related shortness of breath, which can be assessed with the New York Heart Association (NYHA) functional class, computerized axial tomography scan (CAT), or Modified Medical Research Council (mMRC) scales. Physical examination reveals bilateral crackles in the lower lung zones, with some patients reporting wheezing and diminished breath sounds.[3] Combined pulmonary fibrosis and emphysema currently lacks definitive therapy, with treatment still focusing on managing emphysema and fibrosis. Management of emphysema in CPFE predominantly involves therapies similar to those for chronic obstructive pulmonary disease (COPD), such as the use of long-acting β2-agonist (LABA), which can be combined with inhaled corticosteroids.[2] In this case report, we examined the clinical signs observed, the examinations conducted, the therapies provided, and the complications that occur in a CPFE patient.

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CASE

A 44-year-old man with a body mass index (BMI) of 20 kg/m² (normal weight) is a former smoker who quit six years ago after a 28-year smoking history. During this time, he consumed 48 cigarettes daily, sometimes with filters and sometimes without. The patient presented to the Emergency Department in November 2023 with complaints of increased shortness of breath compared to previous exacerbations five months and five years prior. This symptom had worsened for one week before arriving at the Emergency Department, and his shortness of breath was activity-related (mMRC 4). A greenish sputum-producing cough had been present for one month, intermittently disappearing. The cough was not affected by weather or time. The patient did not continue the inhaler prescribed in July but used a short-acting β2-agonist (SABA) nebulizer intermittently when experiencing breathlessness, at a frequency of 7–8 times per day. The patient also did not have regular follow-up appointments at the outpatient clinic.

On examination, the patient's blood pressure was 124/78 mmHg, heart rate was 102 beats per minute, respiratory rate was 30 breaths per minute, and oxygen saturation was 79% on room air, improving to 92% with a 3 liters per minute (LPM) nasal cannula. The patient reported a visual analog scale (VAS) dyspnea score of 7–8. Chest examination revealed intercostal retractions, nasal flaring, prolonged expiration, bronchial breath sounds, and additional sounds such as rales throughout most lung fields. Wheezing was present in both lung fields, characterized by high-pitched, polyphonic sounds.

Table 1. Results of serial arterial blood gas indicating chronic respiratory failure

	Results 26/11/2023 (3 LPM NC)	Results 27/11/2023 (Room Air)	Reference Range
pH	7.359	7.473	7.35–7.45
pCO_2 (mmHg)	65.9	44.4	33–44
pO_2 (mmol/L)	178.8	126.7	71–104
HCO_3 (mmol/L)	37.5	32.8	22–29
Total CO_2 (U/L)	19.9	34.2	23–27
BE (mmol/L)	9.4	8.7	(−2)–(+3)
O_2 saturation (%)	99.7	98.7	94–98

LPM: liters per minute; NC: nasal cannula; BE: base excess

The table indicates metabolic compensation, where despite an increase in pCO_2, elevated base excess (BE) and HCO_3 levels suggest chronic respiratory failure type 2.

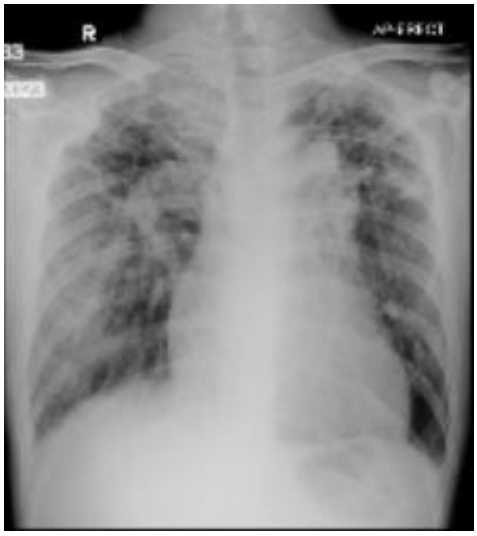


Figure 1. Chest X-ray showed extensive fibrosis in both lungs with emphysema

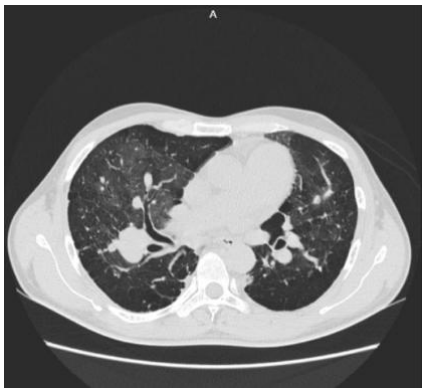
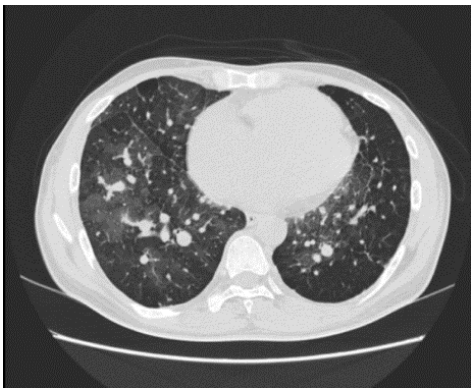
a.  b. 

Figure 2. High-resolution computed tomography (HRCT) (a) showed bullae and panlobular emphysema with nodules; (b) revealed ground glass opacity, reticulation, and calcification. Fibrosis was observed in the apex of the lung fields (mosaic pattern), with no significant change from the HRCT in June 2023.

Table 2. Spirometry results: decreased FVC, FEV1, and FEV1/FVC ratio

Parameter	Pred	LLN	Best	%Pred
FVC	3.36	2.68	1.08	32
FEV1	2.70	2.05	0.47	17
FEV1/FVC	0.805	0.703	0.432	54

FVC: forced vital capacity; FEV1: forced expiratory volume; LLN: lower limits of normal

On radiological and pulmonary function examinations, the changes were not significantly different compared to the assessments in June 2023. Unfortunately, the patient could not continue the diffusing capacity of the lung for carbon monoxide (DLCO) examination due to experiencing exacerbation after the flow-volume loop (FVL) maneuver.

The management provided include nebulized SABA (salbutamol)+short-acting muscarinic-antagonist/SAMA (ipratropium bromide) every 20 minutes for 1 hour, alternated with nebulized fluticasone every 30 minutes for 1 hour, followed by nebulized SABA+SAMA every 6 hours and nebulized fluticasone every 12 hours. Intravenous methylprednisolone 62.5 mg was continued with 32 mg every 12 hours, along with theophylline 150 mg twice daily, acetylcysteine 200 mg three times daily, and spironolactone 50 mg once daily. After 12 days of treatment, the patient was discharged, with a follow-up plan for LABA (olodaterol)+long-acting muscarinic antagonists/LAMA (tiotropium) Respimat inhaler therapy. The patient was discharged in stable condition with improved shortness of breath, having an oxygen saturation of 93% on room air, and was scheduled for follow-up at the outpatient clinic and further follow-up at the pulmonary rehabilitation department with breath stacking.

Hospitalization History

Treatment in 2018

The patient was diagnosed with clinical pulmonary tuberculosis (TB) after a tissue rapid molecular test (TCM) TB examination returned negative results. This diagnosis was made due to chronic complaints, including a productive cough and shortness of breath for 1 month. The patient had been treated for 1 week with no improvement and began taking anti-TB drugs from February to July 2018.

Treatment in 2022

The patient was diagnosed with TB sequelae and moderate exacerbation of COPD in stable COPD group D, as treatment had been completed in 2018. The patient presented with worsening shortness of breath since 2018, influenced by activity (mMRC 2), and was accustomed to using a nebulized SABA jet. A TCM TB examination was again performed with negative results. Treatment was administered for 10 days, including nebulized SABA jet every 8 hours, nebulized budesonide jet every 12 hours, intravenous methylprednisolone 62 mg every 12 hours, and intravenous ceftriaxone 1 g every 12 hours. Additionally, during outpatient care, an inhaler with SABA pressurized metered-dose inhaler (pMDI) and LABA (salmeterol)+inhaled corticosteroid/ICS (fluticasone propionate) accuhaler dry powdered inhaler (DPI) was provided.

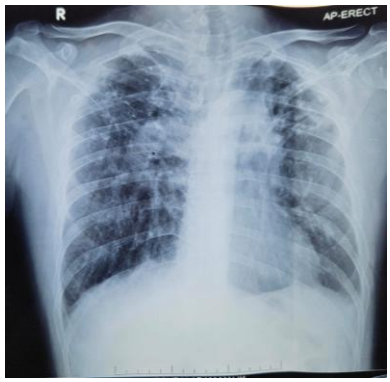


Figure 3. Chest X-ray showed fibrosis in both lungs

Treatment in July 2023

The patient presented to the Emergency Department with chief complaints of increased breathlessness, particularly during activities (mMRC 3), a productive cough with yellow-greenish sputum, and a weight loss of 15 kg over 1 month (weight 42 kg, height 155 cm, BMI 17.48). Night sweats were not reported, and no subfebrile fever was observed. The patient had a history of irregular outpatient clinic visits, and the prescribed inhaler was not used regularly. Instead, the patient relied on a SABA nebulizer approximately 5–6 times daily, especially when experiencing severe breathlessness.

Upon examination, the patient's blood pressure was 110/78 mmHg, heart rate was 111 beats per minute, respiratory rate was 30 breaths per minute, and oxygen saturation was 83% on room air, which improved to 93% with a 5 LPM nasal cannula. The patient reported a VAS dyspnea score of 5–6. Chest examination revealed intercostal retractions, nasal flaring, prolonged expiration, bronchial breath sounds, and additional sounds such as rales throughout most lung fields. Wheezing was present in both lung fields, characterized by high-pitched, polyphonic sounds. The TCM TB examination yielded negative results.

Table 3. Improvement of respiratory acidosis during treatment

	Results 4/7/2023 5 LPM NC	Results 7/7/2023 3 LPM NC	Results 8/7/2023 3 LPM NC	Results 11/7/2023 Room Air	Reference Range
pH	7.291	7.473	7.433	7.470	7.35–7.45
pCO_2 (mmHg)	55.4	46.1	46.6	26	33–44
pO_2 (mmol/L)	107.2	150.9	176.9	194.1	71–104
HCO_3 (mmol/L)	26.9	34.1	32.1	19.1	22–29
Total CO_2 (U/L)	28.6	35.5	33.6	19.9	23–27
BE (mmol/L)	0.1	9.7	7.5	-3.0	(−2)–(+3)
O_2 saturation (%)	97	99.3	99.6	99.7	94–98

LPM: liters per minute; NC: nasal cannula; BE: base excess

At the beginning of treatment, blood gas analysis showed respiratory acidosis, with improvement observed after inhaler therapy, resulting in a final pCO_2 of 26 and a normalized pH.

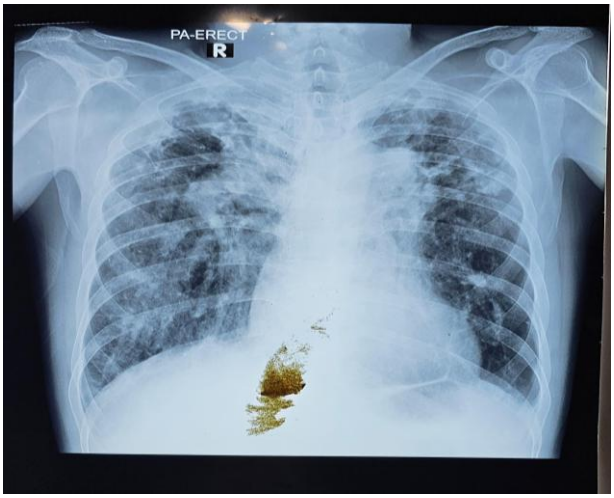
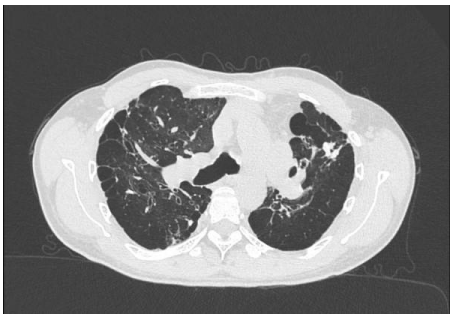
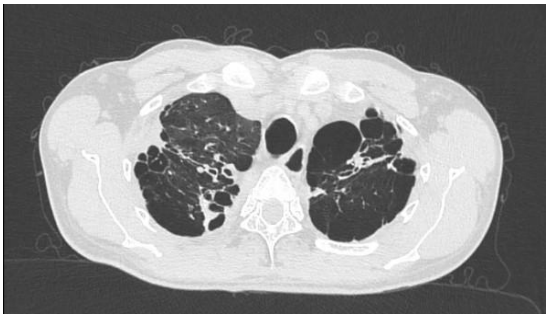


Figure 4. Chest X-ray showed extensive fibrosis in both lungs with emphysema

a.  b. 

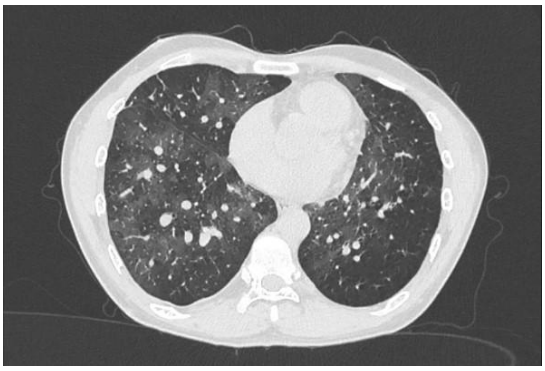
c. 

Figure 5. High-resolution computed tomography (HRCT) (a) showed dominant bullae and panlobular emphysema; (b) showed dominant fibrosis, traction bronchiectasis, and a reticular pattern; (c) showed dominant ground-glass opacities, some calcification, and a mosaic attenuation pattern.

Table 4. Spirometry: decrease in FVC, FEV1, and FEV1/FVC ratio

Parameter	Meas	Pred	%Pred
FVC	0.73	3.83	19.1
FEV1	0.49	3.17	15.5
FEV1/FVC	67.12	83.12	80.8

FVC: forced vital capacity; FEV1: forced expiratory volume

In the radiological examination, the findings resembled ILD, leaning more towards CPFE. The pulmonary function test interpretation supported this, showing restrictive and obstructive patterns. Unfortunately, the DLCO test was not available at the hospital.

Management included nebulized SABA+SAMA every 20 minutes for 1 hour, alternated with nebulized budesonide every 30 minutes for 1 hour. However, the patient could not tolerate nebulized SABA+SAMA due to increased breathlessness with frequent use. Nebulized budesonide was continued every 12 hours, along with intravenous methylprednisolone 125 mg every 24 hours for 2 days, acetylcysteine 400 mg three times daily, intravenous ceftriaxone 1 g every 12 hours, and azithromycin 500 mg orally once daily.

On the second day, after retrying nebulized SABA+SAMA, the patient found it more comfortable. Hence, it was continued every 6 hours and gradually reduced to every 8 hours until it was discontinued as the shortness of breath improved. Steroid tapering was performed daily, starting from 62.5 mg every 12 hours, then 62.5 mg every 24 hours, and then 32 mg every 24 hours, followed by oral administration at 8 mg three times daily. The patient also consulted with the Nutrition Department and received IVFD Aminofluid 1,000 cc per 24 hours. A rehabilitation medicine consultation was conducted, with plans for chest physiotherapy and breathing exercises.

After 8 days of treatment, the patient was discharged with a follow-up plan for LABA+LAMA Respimat inhaler, further follow-up at the pulmonary rehabilitation department, and using long-term oxygen therapy (LTOT)/home oxygen therapy (HOT) at 3 LPM for 15 hours.

DISCUSSION

Emphysema occurring in fibrotic interstitial lung disease, including idiopathic pulmonary fibrosis (IPF), can be referred to as CPFE.[1] This condition was introduced by Cottin in 2005 and is characterized by respiratory symptoms that differ from typical fibrotic diseases. In CPFE, worsening respiratory symptoms are marked by declining lung function and high mortality rates.[2]

In this patient, a deterioration of symptoms has been observed over time, beginning with the initial treatment in 2018, initially diagnosed as TB. Symptoms worsened in 2022 and progressed to acute respiratory failure in 2023, eventually leading to chronic respiratory failure in subsequent treatments. Cottin diagnosed CPFE based on HRCT findings, which typically show a basilar UIP pattern with predominant emphysematous changes in the upper lobes (centrilobular and/or paraseptal).[3] In HRCT of the patient, a combination of

emphysema and fibrosis was observed, though with differing locations: emphysema appeared as panlobular, while fibrosis was more prominent in the apex area, showing a mosaic pattern.

A previous study described emphysema in 40% of cases as scattered across various lung locations, with fibrosis manifesting as honeycombing, reticular opacities, traction bronchiectasis, and ground-glass opacities (GGO).[4] In this patient, fibrosis appeared as traction bronchiectasis, reticular opacities, and GGO.

Combined pulmonary fibrosis and emphysema is often associated with smoking-related lung diseases such as COPD and respiratory bronchiolitis-associated interstitial lung disease (RB-ILD).[2,5] On average, patients have a smoking history of about 40 packs/year, although some CPFE patients do not smoke and may be associated with connective tissue diseases (CTD), such as scleroderma.[3,5] This patient has a history of smoking 48 cigarettes per day for 28 years.

Patients with CPFE commonly experience activity-related shortness of breath, which can be assessed using the NYHA functional class, CAT, or mMRC scales. Physical examination often reveals bilateral crackles in the lower lung zones, with some patients also reporting wheezing and diminished breath sounds.[3] Additionally, CPFE patients may exhibit finger clubbing, hypoxemia, and chest pain. Another important consideration in CPFE is the potential for developing pulmonary hypertension, which can worsen exacerbations and increase mortality, necessitating echocardiographic assessment or right heart catheterization.[3,6]

In this patient, an investigation for pulmonary hypertension has not yet been conducted, but radiological findings suggest that cardiac enlargement has begun. Klebs von den Lungen-6 (KL-6) is a protein expressed by type II alveolar pneumocytes and bronchiolar epithelial cells and is valuable in diagnosing CPFE. KL-6 testing has an 81% sensitivity and 73% specificity for distinguishing CPFE from IPF. Additionally, elevated levels of this biomarker indicate a poorer prognosis and more frequent exacerbations.[4,7]

Spirometry can differentiate between CPFE and IPF. In other fibrotic diseases, there is no decrease in the forced expiratory volume (FEV1)/forced vital capacity (FVC) ratio because no emphysema component is present. However, there may be decreased DLCO values and decreased PaO_2. Combined pulmonary fibrosis and emphysema can also be distinguished from COPD by having a better FEV1/FVC ratio, although both exhibit decreased DLCO.[3] The patient's spirometry showed a decreased FEV1/FVC ratio with decreased FEV1 and FVC, and the DLCO maneuver could not be performed due to limitations. Repeated attempts yielded consistent results.

Another way to differentiate CPFE from other diseases is by using histopathology and bronchoalveolar lavage (BAL) analysis. Histopathologically, a UIP pattern appears as thick-walled cystic lesions (TWCLs) accompanied by emphysema, membrane damage, and thickening of respiratory bronchioles surrounded by fibrosis. Bronchoalveolar lavage analysis shows a leukocyte count of $240\pm200\times10^6$/L, with a differential cell count of macrophages 76%±24 (range 10–90), neutrophils 10%±19 (2–73), eosinophils 2%±10 (0–43), and lymphocytes 5%±9 (0–43).[2,3]

Combined pulmonary fibrosis and emphysema currently lacks definitive therapy, with treatment still focusing on managing emphysema and fibrosis.[2] It is also important to consider the management of gastroesophageal reflux disease (GERD), although the relationship remains controversial.[8] A previous study suggested that untreated GERD can lead to more frequent exacerbations in emphysema-related diseases like COPD.[9]

The management of CPFE predominantly involves therapies similar to COPD, combined with fibrotic therapy such as pirfenidone, along with the administration of LABA, which can be combined with ICS.[2] Regular administration of ICS/LABA can improve lung function, reduce exacerbation frequency, and lower mortality rates during exacerbations.[2,3]

In the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023, there was a shift in therapy guidelines where SABA was no longer recommended for routine use due to its tendency to cause more frequent exacerbations.[10] Therefore, there has been a shift towards the use of LABA.[10] A previous study suggested that routine use of ICS should be considered cautiously regarding patient oral hygiene, as regular use can increase the risk of oropharyngeal candidiasis, hoarseness, and pneumonia.[11]

A study in Sweden involving 20,000 COPD patients found that routine use of SABA was associated with an increased risk of exacerbations and death from various causes within the group using SABA regularly.[12] Criteria for patients who should be monitored for indications of SABA overuse include using more than 2 SABA canisters per year or more than 2 SABA prescriptions per week. Other studies suggested issuing a warning regarding excessive SABA use if a patient uses more than 3 SABA canisters per year.[13,14] If a patient engages in this behavior, consideration should be given to allergens that may trigger it, patient compliance, and the possibility of adding additional therapy.[14]

The patient has been using SABA nebulizers, typically 5–6 respules almost every day, to alleviate

shortness of breath for 2 years without medical supervision. However, despite daily SABA use, the patient's shortness of breath has not improved and has, in fact, worsened over time, prompting the patient to visit the emergency department.

Routine use of SABA and ICS is not recommended. Steroids inhibit the downregulation of β_2 receptors and increase receptor expression.[12,15] Short-acting SABA can lead to increased bronchial responsiveness and decreased tolerance to the bronchodilator effects of β_2 agonists. This forms the basis for the shift in COPD therapy, now recommended as triple therapy: LABA/ICS+LAMA or all three combined (LABA/LAMA/ICS).[10,11,15]

The patient was prescribed LABA/LAMA therapy in July 2023, categorizing them as COPD group E. However, the patient did not adhere to routine follow-up appointments, resulting in inadequate monitoring. In COPD management, systemic corticosteroids are recommended during acute exacerbations but should be administered at appropriate doses. There is no difference in efficacy between injectable and oral systemic corticosteroids.[10,11] A different approach is taken in fibrotic ILD, where high-dose corticosteroids may be administered to prevent disease progression. This is particularly important if the patient is diagnosed with hyperglycemia.[2,11]

Similar measures were taken for the patient after he was no longer experiencing exacerbations. During treatment, the patient, who was initially on high doses, was gradually tapered down to 8 mg of methylprednisolone thrice daily. Chronic obstructive pulmonary disease management is multidisciplinary, with COPD patients also needing to address comorbidities that worsen symptoms and increase the risk of exacerbations. Additionally, COPD management is holistic, beginning with smoking cessation programs, pneumococcal vaccination, and ensuring patient adherence to treatment.[10,16] Several studies have emphasized the importance of treatment adherence in reducing symptoms and exacerbation rates, focusing on inhaler technique, inhaler type, and medication dosage according to the patient's current group.[16,17]

Adherence is difficult to achieve and is influenced by the patient's trust in the doctor and the social support provided during treatment. However, it has been shown to improve the quality of life for COPD patients.[16] The patient has been given appropriate therapy according to his current group. In July 2023, HOT was prescribed, and the patient was scheduled for medical rehabilitation. However, the patient did not attend and missed scheduled follow-up appointments.

Chronic obstructive pulmonary disease patients eligible for HOT include those with a PaO_2 <55 mmHg at rest or 56–59 mmHg if polycythemia (hematocrit >0.55) or clinical and electrocardiographic signs of pulmonary hypertension are present. They are typically prescribed 1–2 LPM for approximately 15 hours daily.[18] A previous study recommended that patients with severe resting hypoxemia due to stable ILD and COPD patients be given ambulatory oxygen and liquid oxygen at rates >3 LPM during exertion.[19]

The patient was suspected to have cardiac impacts, with signs of cardiomegaly. Hence, HOT was prescribed along with medical rehabilitation. It is important to note that oxygen is a medication and should not be adjusted without consulting a doctor. Oxygen toxicity can occur if not properly monitored, and desensitization of chemoreceptors has been reported, leading to increased patient burden.[19,20]

In addition to emphysema management based on COPD therapy, antifibrotic therapy is also crucial in CPFE patients. Although drugs like nintedanib may not have significant effects on emphysema, they can improve FVC values after 52 weeks of use.[2,21] Another therapy frequently prescribed for IPF management is pirfenidone. Its use over 52 weeks has shown significant improvement in patient symptoms. However, no data supports its effectiveness when used concurrently with emphysema therapy in CPFE patients.[3,19]

The patient could not currently be prescribed antifibrotic therapy due to economic constraints and lack of health insurance coverage for these medications. Therefore, the patient was temporarily using steroids and receiving COPD-based management. Lung volume reduction surgery (LVRS) is a final option recommended for patients experiencing worsening symptoms and frequent exacerbations, which can improve quality of life.[2]

CONCLUSION

Combined pulmonary fibrosis and emphysema is rarely recognized conditions and is often associated with other diseases, underscoring the need for further study. The management of CPFE requires a well-balanced combination of treatments targeting both COPD and fibrosis to prevent complications such as pulmonary hypertension. Proper education is essential to prevent patients from receiving incorrect therapies, such as the routine use of SABA.

Consent

The patient provided consent for their condition and disease progression during treatment at Haji Adam Malik General Hospital, Medan, to be used as educational material in the field of medicine. Additionally, the patient was informed about the necessary procedures and interventions that would be undertaken as part of their appropriate treatment plan.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Visualization, data curation, writing, review & editing: FR. Methodology, resources, supervision, validation, writing, and original draft: APT.

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