Clinical and Radiologic Manifestations of Combined Pulmonary Fibrosis and Emphysema (CPFE)

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Learning Objectives

1. To review various important clinical and radiologic manifestations of combined pulmonary fibrosis and emphysema (CPFE)
2. To improve the awareness of CPFE and to help effective therapeutic strategies in clinical practice
Summary of Content

1. Definition
2. Prevalence, Pathogenesis and Etiology
3. Clinical characteristics
4. Radiologic manifestations on CT
5. Complications
6. Prognosis and Mortality
1. Definition of CPFE

- Clinical entity characterized by the coexistence of upper lobe *emphysema* and lower lobe *fibrosis*
1. Definition of CPFE

**CPFE inclusion criteria** by Cottin et al. in 2005: following criteria were met

(1) presence of *emphysema* on CT scan
   - defined as well-demarcated areas of decreased attenuation in comparison with contiguous normal lung and marginated by a very thin (<1 mm) or no wall, and/or multiple bullae (>1 cm) with upper zone predominance

(2) presence of a diffuse parenchymal lung disease with significant pulmonary *fibrosis* on CT scan
   - defined as reticular opacities with peripheral and basal predominance, honeycombing, architectural distortion and/or traction bronchiectasis or bronchiolectasis

(3) focal ground-glass opacities and/or areas of alveolar condensation that could be associated but were not prominent
1. Definition of CPFE

**Exclusion criteria** by Cottin et al. in 2005

- Patients with connective tissue disease (CTD) at the time of the diagnosis of CPFE
- Patients with a diagnosis of other interstitial lung diseases (ILDs)
  - Drug-induced interstitial lung disease
  - Pneumoconiosis
  - Hypersensitivity pneumonitis
  - Sarcoidosis
  - Pulmonary histiocytosis
  - Lymphangioleiomyomatosis
  - Eosinophilic pneumonia
2. Prevalence, Pathogenesis and Etiology

**Prevalence**

- **8% to 51%** of idiopathic pulmonary fibrosis (IPF) patients demonstrate some degree of emphysema
  
  CHEST 2013;144:234–240, CHEST 2012;141:222–231

- **4.4% to 8%** of emphysema patients have some degree of lung fibrosis
  

- **7%** of ILD associated with CTD
  - Systemic sclerosis (SSc); 3%
  - SSc and ILD; 5-10%
  - Rheumatoid arthritis and ILD; 12–20%

Arthritis Rheum 2011;63:295-304
2. Prevalence, Pathogenesis and Etiology

Pathogenesis
- The exact mechanism which leads to the coexistence of pulmonary *fibrosis* and pulmonary *emphysema* has not been fully understood.

Ann Transl Med 2016;4:196

Etiology (risk factor)
- **Cigarette Smoking**: strong association
  - 592/607 (98%); current or former smokers
- **Male gender**
  - Male predominance
  - 529/587 (90%); men

CHEST 2012;141:222–231
2. Prevalence, Pathogenesis and Etiology

- **Occupational Exposures**
  - Asbestosis; emphysema were present (10%-36%)  
    - AJR 2003;181:163-169
  - Coal dust exposure  
    - Occup Environ Med 1994;51:400-407
  - Mineral dust exposure
    - agrochemical compounds, tyre industry worker, welder
  - CTD-associated CPFE
    - more likely to be woman, significantly younger
    - tend to have less severe outcomes than their idiopathic CPFE
    - lower prevalence of pulmonary hypertension

- **Other Associations**
  - Hypersensitivity pneumonitis/farmer lung  
    - Eur Respir J 2000;16:56-60
  - CTD-associated CPFE
    - J Thorac Dis 2015;7:767-779
3. Clinical characteristics

A. Symptoms: Cough, dyspnea

- Chronic obstructive pulmonary disease (COPD): chronic cough with daily variable sputum production and progressive dyspnea
- IPF: dyspnea is the primary symptom existing over 90% of patients at the time of diagnosis
  - followed by frequent dry and nonproductive cough experienced by 73-86% of patients in the late stage
- CPFE: more similar to IPF
  - especially exertional dyspnea (exists in almost all the patients; functional class III to IV of the New York Heart Association)
3. Clinical characteristics

B. Pulmonary function test findings

- **Preserved lung volume**
  - the counterbalancing effects of the restrictive defect of pulmonary fibrosis and the propensity to hyperinflation seen in emphysema

- **Marked reduction in diffusing capacity for carbon monoxide (DLco)**
  - reduced vascular surface area and pulmonary capillary blood volume plus alveolar membrane thickening resulting from the two coexistent disease processes
4. Radiologic manifestations on CT

- Total *emphysema* score at a **threshold of 10%** to indicate patients with CPFE
  - 10% threshold corresponds to **GOLD** (Global Initiative for Chronic Obstructive Lung Disease) stage II or worse in patients with isolated **COPD**
  - Suggesting that this amount of *emphysema* is expected to have **symptomatic** and physiologic consequences

- CPFE: coexistence of **significant emphysema** of **grade 2 or more** (%LAA ≥ 25%) and diffuse parenchymal lung disease with **significant pulmonary fibrosis**

*CHEST 2013;144:234–240*
*Respirology 2010;15:265–271*

%LAA = %low attenuation area
A. Emphysema

- Mix of all 3 types of emphysema are noted in the upper lobes
  - **Centrilobular** emphysema (97%): m/c
  - **Paraseptal** emphysema (93%)
    - much more frequently among patients with CPFE than those with emphysema alone (33.3% vs 8.5%, respectively)
  - **Bullae** (54%)

A. Emphysema

- Degree of *emphysema* based on CT *emphysema* scores
  - Similar to those with mild to moderate *emphysema*
  - Lower than those with severe *emphysema*
  - Total *emphysema* scores were reported the highest in COPD and higher in CPFE than in IPF

- Extent of *emphysema* was greater in CPFE patients with thick-walled cystic lesions (TWCLs) compared with those without such lesions
B. Fibrosis

- Features of pulmonary *fibrosis*
  - **Honeycombing**: m/c feature (75.6–95%)
  - **Reticulation** (84.4–87%)
  - **Traction bronchiectasis** (40–69%)

B. Fibrosis

- *Fibrosis* scores: generally higher in CPFE and *IPF* than that in *COPD*

- The difference of *fibrosis* scores between CPFE and *IPF*: controversial
  - CPFE shows a *high* HRCT fibrotic score
  - CPFE did *not* show significant difference on fibrotic scores
    - similar extent of fibrosis in two groups
  - CPFE has a *lower* fibrotic score

*Eur Respir Rev 2013;22:153-7*
*Chin Med J 2014;127:469-74*
*CHEST 2013;144:234–240*
C. Thick-walled cystic lesions (TWCL)

- **Unique** radiological and pathological features of **CPFE** (72.7%)
  - not in any patient with either **IPF** or **emphysema** alone

**Definition**

- **Radiological:** cysts measuring at least 1 cm in diameter and delineated by a 1-mm-thick wall in an area of the lung where reticulation and/or honeycombing was evident on CT images.

- **Pathological:** cystic lesions at the level of membranous bronchiole with dense fibrous wall, destruction of respiratory bronchiole and alveoli, and occasional fibroblastic foci.
  - often apposed to honeycomb lesion

- **Enlargement** of TWCLs: thought to reflect the worsening of interstitial fibrosis and progression of the disease.
D. Ground glass opacity (GGO)

- Areas of ground glass attenuation (62.2-66%)
  - Commonly present, as in 66% of subjects with CPFE in a series by Cottin et al.
  - GGO may be indicative of smoking-related interstitial lung diseases, such as desquamative interstitial pneumonia

61-year-old men with desquamative interstitial pneumonia.
Fig 1. A 62 year-old-male patient with combined pulmonary fibrosis and emphysema (CPFE).

(A) Both upper lobes show centrilobular and paraseptal emphysema and bullae. (B) Both lower lobes show reticular opacities with peripheral and basal predominance and honeycombing, representing typical usual interstitial pneumonia (UIP) pattern. (C) Right lower lobe shows thick-walled cystic lesion (TWCL) with internal septations (arrow) and larger than honeycombing. (D) Spirometry graph shows mild obstruction. (FEV₁/FVC = 66%, FEV₁ = 2.28 liters, which was 74% of predicted value)
Representative case 2

Fig 2. A 43 year-old-male patient with combined pulmonary fibrosis and emphysema (CPFE).

(A) Both upper lobes show paraseptal emphysema and bullae. (B, C) Both lower lobes show reticular opacities and traction bronchiectasis with peripheral and basal predominance representing nonspecific interstitial pneumonia (NSIP) pattern. (D) Spirometry graph shows minimal obstruction. (FEV₁/FVC= 74%, FEV₁ = 3.17 liters, which was 79% of predicted value)

FEV₁ = Forced expiratory volume in 1 second, FVC= forced volume vital capacity.
5. Complications

A. Pulmonary arterial hypertension (PH)

- More common in CPFE (47% to 90%) than in emphysema (10% to 30%) and advanced IPF (31% to 46%)

- Prognosis: 1-YSR of only 60% was reported in a study involving 40 CPFE patients with PH confirmed by right heart catheterization

- Treatment

  - **Pulmonary vasodilators**: a possibility of worsening hypoxemia exists due to ventilation-perfusion mismatch
  - **Oxygen therapy**
  - **Lung transplantation**
    - most reasonable measures for the management of PH in CPFE syndrome

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I-YSR = 1 year survival rate

**Eur Respir J 2010;35:105-11**

**Ann Transl Med 2016;4:196**
5. Complications

B. Lung cancer

- Patients with **CPFE** develop lung cancer more commonly (35.8% to 46.8%) than patients with **IPF** (22.4% to 31.3%) and those with **emphysema** alone (6.8% to 10.8%)

- **Squamous cell carcinoma**: m/c histologic type in CPFE

- **Location**
  - CPFE and **IPF**: predominantly occurs in the **subpleural** areas
  - **COPD**: occurs more frequently in the **lung apices**
    - **emphysema** by itself might not contribute as much as lung **fibrosis** to the development of lung cancer in CPFE
5. Complications

C. Acute lung injury (ALI)

- Very high incidence of ALI after lung resection surgery or chemotherapy has been noted
- Up to 70% of post-lobectomy ARDS; have preexisting CPFE
  
  Kazuhiro et al.
  - Among 101 patients with CPFE and lung cancer
  - 19.8% incidence of ALI following definitive lung cancer therapy (20/101)
  - Surgical resection: m/c cause of acute exacerbation (9/33, 27.3%)
  - Chemotherapy (12/60, 20%)
  - Radiation alone (1/6, 16.7%)

ARDS = Acute respiratory distress syndrome
Representative case 3

Fig 3. A 75 year-old-male patient with combined pulmonary fibrosis and emphysema (CPFE).
(A) Both upper lobes show paraseptal and centrilobular emphysema and bullae. (B) Pulmonary trunk dilatation suggesting pulmonary arterial hypertension. (C) Both lower lobes show reticular opacities and traction bronchiectasis with peripheral and basal predominance representing nonspecific interstitial pneumonia (NSIP) pattern.
Fig 4. A 65 year-old-male patient with combined pulmonary fibrosis and emphysema (CPFE).

(A, B) Initial CT scans show centrilobular and paraseptal emphysema in predominantly both upper lobes, reticular opacities with ground glass opacities in both lower lobes subpleural area and subtle nodular increased opacity in right upper lobe subpleural area (arrow). (C, D) Follow up CT scans after 2 years and 3 months show a lobulated nodular lesion with pleural tagging in right upper lobe subpleural area (arrow). Percutaneous needle biopsy was performed and pathologically proven as adenocarcinoma. The extent of upper lobe emphysema and lower lobe fibrosis shows no significant interval change.
### 6. Prognosis and Mortality

- Poor survival statistics, **worse** than those with pulmonary *fibrosis* or *emphysema* alone
- Mortality in the CPFE: significant but **controversial**

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- 5-YSR: 35–80%
- Median survival: ranging between 2.1 to 8.5 years

NR = not reached

5-YSR = 5 year survival rate
6. Prognosis and Mortality

- Poor survival statistics, worse than those with pulmonary fibrosis or emphysema alone

- Mortality in the CPFE: significant but controversial
  - No clear difference in survival in CPFE vs. IPF alone
  - Chest 2012;141:222–231
  - Worse survival in CPFE vs. isolated IPF
    - related to pulmonary hypertension
    - Chest 2009;136:10-15
  - Comparable or better survival in CPFE cohorts than in groups with isolated pulmonary fibrosis
    - Fibrogenesis Tissue Repair 2011;4:6
In conclusion

- Combined pulmonary fibrosis and emphysema (CPFE) is a clinical syndrome characterized by the coexistence of upper lobe emphysema and lower lobe fibrosis.
- Patients with CPFE may have severe dyspnea and impaired gas exchange with preserved lung volumes.
- CPFE shows different natural history and prognosis than IPF or emphysema alone.
- Correct and early recognition of this syndrome and early diagnosis of its complications are important for providing the patients with the best treatment.
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• Abstract Submission      by May 31 (Wed)
• Abstract Acceptance Notice  on July 5 (Wed)
• Presenter Registration    by July 31 (Mon)
• Early Registration        by July 31 (Mon)
• Pre-registration           by August 31 (Thu)
• Hotel Reservation          by August 31 (Thu)

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