**Combined pulmonary fibrosis and emphysema (CPFE) syndrome, desquamative interstitial pneumonia (DIP), and respiratory bronchiolitis with interstitial lung disease (RB-ILD)**

Vincent Cottin  
National Reference Center for rare pulmonary diseases  
University of Lyon  
28 Avenue du Doyen Lepine  
69677 Lyon  
France  
www.maladies-pulmonaires-rares.fr  
vincent.cottin@chu-lyon.fr

**AIMS**

- To know the spectrum of smoking-related interstitial lung diseases (ILDs).
- To be able to diagnose and manage RB-ILD and DIP.
- To be able to recognise pulmonary Langerhans cell histiocytosis.
- To understand the main characteristics and consequences on management of the syndrome of CPFE.

**SUMMARY**

The smoking-related interstitial lung diseases (ILDs) comprise several diseases that share a strong causal relationship with tobacco smoking, and may coexist and/or be associated with emphysema.

They include the traditional smoking-related ILDs (respiratory bronchiolitis–associated ILD, RB-ILD; desquamative interstitial pneumonia, DIP; and pulmonary Langerhans cell histiocytosis) and the syndrome of combined pulmonary fibrosis and emphysema (CPFE), more recently individualized. Some authors also include in this group entities that are linked to tobacco smoking but can occur in a different etiological context such as acute eosinophilic pneumonia (box 1) [1], or rheumatoid arthritis-associated ILD.

**Box 1 Proposed classification of smoking-related ILDs**

**Group 1: chronic ILDs that are very likely caused by cigarette smoking**
- Respiratory bronchiolitis–associated ILD
- Desquamative interstitial pneumonia
- Adult pulmonary Langerhans cell histiocytosis

**Group 2: acute ILDs that may be precipitated by cigarette smoking**
- Acute eosinophilic pneumonia
- Pulmonary hemorrhage syndromes

**Group 3: ILDs that are statistically more prevalent in smokers**
- Idiopathic pulmonary fibrosis
- Rheumatoid arthritis–associated ILD

**Group 4: ILDs that are less prevalent in smokers**
- Hypersensitivity pneumonitis
- Sarcoïdosis
Key characteristics of smoking related ILDs

The key characteristics of chronic smoking related diffuse lung disease are listed in table 1 [1] and on the following page [2].

<table>
<thead>
<tr>
<th></th>
<th>RB-ILD</th>
<th>DIP</th>
<th>PLCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association with Cigarette Smoking</td>
<td>95%</td>
<td>60%–90%</td>
<td>95%–97%</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Chronic cough and dyspnea, inspiratory crackles</td>
<td>Chronic cough and dyspnea, inspiratory crackles</td>
<td>Chronic cough and dyspnea. Pneumothorax in 15%</td>
</tr>
<tr>
<td>High-Resolution Computed Tomographic Findings</td>
<td>Centrilobular nodules and ground-glass opacities</td>
<td>Ground-glass and reticular opacities</td>
<td>Peribronchiolar nodules, cavitated nodules, and cysts with relative sparing of lung bases</td>
</tr>
<tr>
<td>Key Histologic Findings</td>
<td>Pigment-laden macrophages in the respiratory bronchioles and alveolar ducts</td>
<td>Diffuse alveolar filling with pigment-laden macrophages</td>
<td>Bronchiolocentric nodules, stellate lesions, CD1a-positive Langerhans cells</td>
</tr>
<tr>
<td>Response to Corticosteroids</td>
<td>Modest, variable</td>
<td>Modest, variable</td>
<td>Modest, variable</td>
</tr>
</tbody>
</table>

Abbreviations: DIP, desquamative interstitial pneumonia; PLCH, pulmonary Langerhans cell histiocytosis; RB-ILD, respiratory bronchiolitis–associated interstitial lung disease.
<table>
<thead>
<tr>
<th>Smoking %</th>
<th>PLCH</th>
<th>RB-ILD</th>
<th>AEP</th>
<th>DIP</th>
<th>CPFE</th>
<th>IPF</th>
<th>RA-ILD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;90</td>
<td>3rd and 4th decades</td>
<td>100</td>
<td>90</td>
<td>100</td>
<td>41-83</td>
<td>5th-6th decades</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>1:1</td>
<td>Slight male dominance</td>
<td>2:1</td>
<td>Nearly 2:1</td>
<td>Rare</td>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>Occurrence in children</td>
<td>Rare</td>
<td>No</td>
<td>Yes</td>
<td>Rare</td>
<td>No</td>
<td>Rare</td>
<td>No</td>
</tr>
<tr>
<td>Onset</td>
<td>Insidious</td>
<td>Dyspnea and cough</td>
<td>Acute</td>
<td>Insidious</td>
<td>Dyspnea and cough</td>
<td>Insidious</td>
<td>Dyspnea and cough</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crackles</td>
<td>Usually absent</td>
<td>50%</td>
<td>60%</td>
<td>Nearly all</td>
<td>50-70%</td>
<td>Lower lobe interstitial lung disease</td>
<td></td>
</tr>
<tr>
<td>Clubbing</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Nearly 50%</td>
<td>50-70%</td>
<td>Upper lobe emphysema associated with lower lobe fibrosis</td>
<td></td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Intermittent/cystic nodular with basilar sparing</td>
<td>Intermittent or normal</td>
<td>Patchy opacities</td>
<td>Intermittent, patchy ground glass</td>
<td>Intermittent, honeycombing with basilar predominance</td>
<td>Lower lobe interstitial lung disease</td>
<td></td>
</tr>
<tr>
<td>HRCT</td>
<td>Nodules and cysts; basilar sparing</td>
<td>Patchy ground glass</td>
<td>Patchy opacities /ground glass</td>
<td>Ground glass with lower lung predominance</td>
<td>Upper lobe emphysema associated with interstitial honeycombing</td>
<td>Subpleural honeycombing, basilar predominance</td>
<td></td>
</tr>
<tr>
<td>Pulmonary function</td>
<td>Obstructive or restrictive</td>
<td>Mixed defect or normal</td>
<td>Restrictive</td>
<td>Restrictive</td>
<td>Mixed defect or normal</td>
<td>Restrictive</td>
<td>Restrictive</td>
</tr>
<tr>
<td>Treatment</td>
<td>Smoking cessation, steroids?</td>
<td>Smoking cessation, steroids</td>
<td>Steroids</td>
<td>Smoking cessation, steroids</td>
<td>Bronchodilators and inhaled steroids</td>
<td>Pirenidone?</td>
<td>Steroids and immunosuppressive treatment</td>
</tr>
<tr>
<td>Response to steroids</td>
<td>Fair</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Poor</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Poor</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Complete recovery possible</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

PLCH: pulmonary Langerhans’ cell histiocytosis; RB: respiratory bronchiolitis; AEP: acute eosinophilic pneumonia; DIP: desquamative interstitial pneumonia; CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; RA: rheumatoid arthritis; HRCT: high-resolution computed tomography. Modified from [26].
The syndrome of combined pulmonary fibrosis and emphysema

There is an increasing awareness of comorbid conditions frequently associated with idiopathic pulmonary fibrosis (IPF), including emphysema, cardiovascular disease, thromboembolic disease, and obstructive sleep apnoea. Recent retrospective data suggest that 21 to 33% of patients with IPF may have coexisting emphysema. The association of emphysema to IPF has been coined the combined pulmonary fibrosis and emphysema (CPFE) syndrome to account for characteristic clinical, functional, imaging, and outcome features. Characteristics of patients with the CPFE syndrome include male predominance, tobacco smoking, severe dyspnea, subnormal spirometry findings, severely impaired transfer capacity for carbon monoxide, hypoxemia at exercise, high frequency of paraseptal emphysema, and a high probability (30-50%) of severe pulmonary hypertension impacting prognosis.

CPFE is a syndrome with characteristic presentation, including very low diffusion capacity contrasting with subnormal spirometry, occurring in heavy smokers with severe dyspnea and exercise limitation. It may be overlooked because of subnormal lung volumes, however gas exchanges are severely altered. Despite moderate or severe emphysema, a large proportion of patients with CPFE have FEV1/FVC > 70% indicating that GOLD criteria for chronic obstructive lung disease may not be applicable. In addition, diagnostic criteria of IPF may not apply, owing to difficulties to ascertain honeycomb changes in patients with associated emphysema UIP and a high frequency of mild to moderate ground glass opacities. The CPFE syndrome may occur in the context of connective tissue disease especially rheumatoid arthritis.

A limited amount of data is available regarding lung pathology in patients with CPFE. Indeed, severe alteration of gas exchange and emphysema features at imaging may explain that lung biopsy is rarely performed, as in the present case. A variety of pathology patterns of pulmonary fibrosis has been reported in patients with CPFE, including predominantly UIP pattern, however nonspecific interstitial pneumonia, desquamative interstitial pneumonia (with extensive fibrosis), respiratory bronchiolitis – associated interstitial lung disease, airspace enlargement with fibrosis, or unclassifiable smoking-related interstitial fibrosis may be observed.

The natural course of disease in CPFE may encompass episodes of acute exacerbation of pulmonary fibrosis, a complication seldom reported previously in CPFE. The presence of significant emphysema impacts FVC measurement, and thus changes in FVC alone may not be a reliable indicator of disease. Patients with CPFE should be excluded from IPF clinical trials. In fact, a decline in FEV1 by 10% or more at 6 or 12 months may be useful in assessing progression of disease, contrasting with monitoring of lone IPF using serial changes in FVC and DLco. The main predictor of subsequent mortality is precapillary pulmonary hypertension that portends a dismal prognosis. Whether survival of patients with IPF is impacted by coexistent emphysema (e.g. CPFE) is controversial due to difficulties in controlling for severity. A composite physiologic index may account for disease severity.

There are no recommendations for treatment of pulmonary fibrosis, emphysema or pulmonary hypertension in the setting of CPFE. It is unknown if treating these components of disease influences clinical outcomes. Patients with CPFE are likely to require long-term oxygen therapy. Isolated observations indicate that therapy specific for pulmonary hypertension may improve hemodynamics, but the potential clinical and survival benefit is unknown. Recent data have recommended against combination therapy with prednisone, azathioprine, and high-dose N-acetylcysteine in IPF, however corticosteroids may still have a role in selected patients with a pathologic pattern of nonspecific interstitial pneumonia. The potential benefit of anti-fibrotic drugs (pirfenidone, nintedanib) in patients with CPFE has not been specifically evaluated.
REFERENCES

Selection of references
- Classification [3]
- Smoking related ILD in general [1, 2, 4]; imaging [5]
- DIP [6] and RB-ILD [7-9]
- PLCH [10], [11, 12], [13-16]
- CPFE [17-34]


EVALUATION

1. In the revised 2013 ATS/ERS classification of idiopathic interstitial pneumonias, which of the followings belong to the group of smoking-related interstitial lung diseases?
   a) Idiopathic nonspecific interstitial pneumonia (NSIP)
   b) Respiratory bronchiolitis-interstitial lung disease (RB-ILD)
   c) Desquamative interstitial pneumonia (DIP)
   d) Pulmonary Langerhans cell histiocytosis (PLCH)
   e) Combined pulmonary fibrosis and emphysema (CPFE)

   Answers B,C

2. In desquamative interstitial pneumonia (DIP), which of the followings are correct:
   a) 60-90% of patients are smokers
   b) Most patients are asymptomatic
   c) Typical HRCT findings are prominent centrilobular nodules and ground glass opacities
   d) Alveolar spaces are diffusely filled with pigment-laden macrophages
   e) Response to corticosteroids is usually good

   Answers : A,D

3. In patients with pulmonary Langerhans cell histiocytosis, which of the following treatments can be considered
   a) Smoking cessation
   b) Cladribine
   c) Macrolide therapy
   d) Pleurodesis in case of pneumothorax
   e) Lung transplantation

   Answers : A,B,D,E

4. In patients with the syndrome of combined pulmonary fibrosis and emphysema, which of the following are correct
   a) All patients are smokers or ex-smokers
   b) The syndrome may occur in patients with rheumatoid arthritis
   c) The main determinant of prognosis is precapillary pulmonary hypertension
   d) There is good evidence that patients should be treated similarly as those with idiopathic pulmonary fibrosis
   e) Genetic testing may contribute to the diagnosis.

   Answers : B,C