Diffuse smoking-related lung diseases: insights from a radiologic-pathologic correlation

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Abstract

Cigarettes are well-recognized risk factors responsible for the emergence of a variety of pathologic conditions affecting both the airways and the lungs. Smoking-related lung diseases can be classified as chronic obstructive pulmonary disease (COPD) and several types of interstitial diseases, such as pulmonary Langerhans cell histiocytosis, bronchiolitis, desquamative interstitial pneumonitis, acute eosinophilic pneumonia, and interstitial fibrosing lung diseases. The evidence of combined lower lung fibrosis and predominant upper lung emphysema is renowned as a distinct clinical entity, named combined pulmonary fibrosis and emphysema. Although computerized tomography permits an adequate classification and distinction of these diseases, the clinical, imaging, and histological features often overlap and coexist in a single patient. Therefore, a combined radiologic and pathologic approach, in the appropriate clinical setting, is useful for best comprehension and distinction of these entities. Our goals are to describe the imaging features in smoking-related lung diseases and how the pathological manifestations translate on high-resolution computerized tomography.

Keywords: Smoking, Emphysema, Bronchitis, Interstitial lung diseases, Fibrosis

Key points

- COPD is one of the most common smoke-related causes of death, depicted by the spirometric evidence of irreversible and usually progressive airflow limitation. It includes chronic bronchitis and emphysema. The peripheral and smaller airways are also affected in both number and caliber.
- Changes in smoking habits are known inducers of the development of acute eosinophilic pneumonia (AEP): initiation of smoking habit, resumption after interruption, and increased frequency of smoking.
- Pulmonary Langerhans cell histiocytosis (PLCH) is an uncommon disease virtually exclusive of smokers. Over time, the cellular nodules are replaced by polymorphic fibrotic scars associated with distorted and enlarged air spaces.
- Besides the difference of imaging findings, desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis/respiratory bronchiolitis-interstitial lung disease (RB/RB-ILD) are a spectrum of the same pathologic event, characterized by the excess of macrophages in the distal airways.
- Fibrosis is also a common radiological feature ranging from sparse fibrosis along the alveolar walls, termed AEF, to a pattern of diffuse interstitial fibrosis, which can represent usual interstitial pneumonia (UIP) in some cases.

Introduction

Cigarettes are a noxious mixture containing around 5000 chemicals and considered as one of the most important causes of chemically mediated disorders in humans. Both direct toxicity and induced immune-mediated response lead to both reversible and irreversible damage from central airways to most distal airways and lung parenchyma [1–3].

The most common smoking-related causes of death include numerous types of cancer, particularly lung cancer, and chronic obstructive pulmonary disease (COPD). Adding to these disorders, cigarettes are a well-known etiologic factor linked with the development of some...
types of interstitial lung disease (ILD), namely AEP, DIP, RB-ILD, and PLCH. Smoking is also responsible for the development of fibrotic lung disease [4–7]. These lung diseases related to smoking are a spectrum of the same pathologic process. Pathologists usually find a mixture of histopathological patterns and a single diagnosis is often difficult to make [5]. Although the majority of the smokers have a certain degree of inflammatory changes in the airways, just a subgroup of individuals develops clinically relevant respiratory disease. Both genetic and exogenous triggers, such as allergens or infections, may be implicated in the development of the disease [7].

In this article, we describe and illustrate the characteristic clinical features, imaging findings, and pathologic findings of diffuse lung diseases related to smoking, encompassing COPD and ILDs. We emphasize the need of a multidisciplinary approach (clinical, radiological, and pathological) for better comprehension and distinction of these entities.

Discussion
Chronic obstructive pulmonary disease
COPD is depicted by the spirometric evidence of irreversible and usually progressive airflow limitation. The disease comprehends distinct however overlapping obstructive disorders, such as chronic bronchitis, emphysema, and also affecting the distal airways of the lung, with both reductions in the number and the caliber. Bronchiolitis is the earliest lesion in COPD, with narrowing and loss of terminal bronchioles preceding emphysematous changes [3, 8]. Emphysema results from permanent enlargement and wall destruction of the airways distal to the surviving terminal bronchioles, progressing in severe cases to coalescence of destroyed lobules [8, 9]. Centrilobular and panlobular emphysema have clinical significance, often associated with increased dyspnea and poorer functional capacity. Additionally, centrilobular emphysema is related to smoking habits, and panlobular emphysema is associated with low body mass index (BMI). Paraseptal emphysema is more common in men and is frequently of little physiologic significance, except for the development of pneumothorax secondary to the presence of paraseptal bleb/bulla [10]. Visual CT evaluation is considered the clinical gold standard for the assessment and characterization of centrilobular and panlobular emphysema, also demonstrated to be valid regarding the pathologic assessments [10–14].
Chronic bronchitis consists in the presence of inflammation in the large airways. Clinically, patients present with chronic cough and sputum during at least 3 months per year in two consecutive years [15]. Chronic bronchitis is triggered and sustained by the activation of an abnormal immune response due to long-term cigarette smoking, causing overproduction of mucus from goblet cells, thickening, and fibrosis of the bronchial walls (Fig. 1). The condition promotes a further reduction of the caliber of the airways, predisposing expiratory collapse. Imaging depicts wall thickening of the large airways, and endobronchial mucus plugging may also be depicted (Fig. 2)[15, 16]. Bronchial wall thickening is consistently associated with a decline in FEV1 and with the risk of acute exacerbation and hospitalization [16–19].

Centrilobular emphysema (CLE) results from an abnormal dilatation of the airspaces distal to the terminal bronchioles. This subtype of emphysema is strongly related to cigarette smoking with higher airway inflammatory cell content and usually with upper lung predominance [10]. CLE originates from the destruction and dilatation of bronchioles, with further coalescence of several primary lesions (Fig. 3). On imaging, small well or poorly demarcated regions of low attenuation can be depicted, surrounded by areas of the normal lung [3, 8–10]. Fleischner Society’s guideline scoring of CLE [20] characterizes emphysema as trace when involving less than 0.5% of a lung region, mild when concerning 0.5–5%, and moderate if more than 5% (Fig. 4). Severe emphysema is classified as confluent (coalescence of centrilobular lucencies) or advanced destructive emphysema (ADE) if the expansion of the entire secondary lobule, distortion of the pulmonary architecture, and splaying or decreased caliber of vessels are present (Fig. 5).

Panlobular emphysema (PLE) like ADE indicates destruction across the lobule. This type of emphysema presents in a younger age group (30–44 years of age). The findings are lower lung predominant in about two-thirds of the individuals (Fig. 6) [3, 8–10, 20]. It is commonly linked to a mutation in the alpha 1-antitrypsin gene, in which Z allele accounts for approximately 95% of clinically recognized cases, causing unopposed action of neutrophil elastase with consequent destruction of lung parenchyma [21].

Acute eosinophilic pneumonia

AEP is an uncommon condition that occurs most frequently in males between the second and forth decades of life. Approximately two-thirds of patients have smoking habits [22–25]. Changes in smoking habits are known inducers of the development of AEP: initiation of smoking habit, resumption after interruption, and increased frequency of smoking [26–28]. The clinical presentation is generally unspecific, letting the disease be frequently misdiagnosed as other most
common entities such as community-acquired pneumonia. The clinical symptoms are acute, with duration of the respiratory illness of less than a month, and characterized by moderate fever, cough, dyspnea, pleuritic pain, malaise, myalgia, and night sweats. Acute respiratory failure is frequent and mechanical ventilation is often required [22, 25]. Therefore, the disease is severe, and most patients fulfill diagnostic criteria for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The key to diagnosis is evidence of eosinophilia in the bronchoalveolar lavage (BAL), with more than 25% of eosinophils on the cell count. Nevertheless, blood eosinophils are frequently at normal levels at the beginning of the clinical presentation and may rise after a few days. BAL is sterile with no bacterial growth during the disease course [22, 23, 25].

Lung biopsy is usually not needed to meet the diagnosis. It shows alveolar and interstitial eosinophilia and alveolar damage. Additional features include nonnecrotizing perivascular inflammation, eosinophilic abscesses, interstitial lymphocytes, organizing fibrinous exudate in the alveoli, type II pneumocyte hyperplasia, and also involvement of the airway [22, 29].

Imaging findings are predominant in the lower lungs, showing diffuse consolidations, ground-glass opacities (GGO), ill-defined centrilobular nodules, smooth septal thickening, and unilateral or bilateral pleural effusion (Fig. 9). The radiologic differential includes infection, fluid overload, ALI/ARDS, hypersensitivity to drugs, and pulmonary hemorrhage [7, 24, 25, 29, 30]. Treatment with steroids achieves an excellent response, with resolution within days of the immunologic process [22, 23].

Pulmonary Langerhans cell histiocytosis
PLCH is an unusual respiratory disease found most commonly in young adults between the third and fourth decades of life. It is exceedingly rare in children and occurs in most cases as a part of disseminated LCH secondary to an abnormal immune response. Over 95% of PLCH patients are smokers and it is estimated that the disease affects approximately 3–4% of smokers. PLCH affects both genders equally [31–33]. Patients usually report fatigue, weight loss, exertional dyspnea, and non-productive cough. Pneumothorax may be the first sign in 15–20% of patients. Although, approximately 20% of patients reported no symptoms at the time of disease detection [33].

Histopathologic findings reveal bronchiole-centered, stellate nodules, containing Langerhans cells, and interspersed with other inflammatory cells (lymphocytes, macrophages, monocytes). Langerhans cells are quite large cells, containing pale cytoplasm and convoluted nucleus, which
Fig. 7 Subtypes of PSE according to the Fleischner Society guidelines on HRCT.  

a Axial CT shows mild PSE (white arrows) with up to 1 cm juxtapleural well-demarcated lucencies.  
b Axial CT depicts substantial PSE, defined as cyst-like lucencies or bullae greater than 1 cm adjacent to the pleura. The patient had spontaneous pneumothorax and black arrow depicts a chest drain. Subcutaneous emphysema is also visible in the right thoracic wall.

Fig. 8 Bullous emphysema in a 55-year-old man.  
a Posteroanterior (PA) radiograph shows lucencies in the superior half of the right hemithorax and in the upper left hemithorax.  
b Axial CT shows upper lobe predominant bullae (asterisks) in the subpleural surface of the right lung. Moderate CLE is also present (arrow).

Fig. 9 Radiologic-pathologic correlation of AEP.  
a Posteroanterior (PA) radiograph shows bilateral ground-glass opacities and consolidation in the mid-left lung zone. A small left pleural effusion is present.  
b Axial CT shows peripheral lower lobe consolidations and ground-glass opacities, mainly on the left.  
c Transthoracic lung biopsy showing eosinophils (black arrow) infiltrating the interstitium and the alveolar spaces; edema (green arrow) and reactive pneumocytes are seen; no necrotizing vasculitis is observed (H&E, × 400).

Fig. 10 Pulmonary Langerhans cell histiocytosis in a 40-year-old man.  

a Axial CT image shows upper lobe predominance of nodules and cysts of varying wall thickness and irregular margins. Arrow depicts a stellate cellular nodule.  
b Transthoracic lung biopsy of the nodule highlighted in a shows a nodular aggregate of cells (lymphocytes, eosinophils, plasma cells, and Langerhans cells) centered in bronchioles (arrow) and extending to the interstitium (H&E, × 200).  
c CD1a immunostaining highlights the Langerhans cells (CD1a, × 100).
resemble coffee grains. They are immunoreactive with CD1a and S-100. Along the disease course, cellular nodules evolve from mixed cellular and fibrotic nodules to entirely polymorphic scars associated with enlarged and distorted air spaces [32–38].

Imaging reveals upper and middle lung predominance of nodules and cysts with variable wall thickness and irregular margins. The disease characteristically spares the costophrenic sulci, extreme apices, and part of the middle lobe and lingula. Imaging findings have a typical progression over time from a predominant nodular pattern to diffusely distributed cysts with bizarre shapes (Fig. 10). The later disease stage is associated with significant emphysematous areas either related to PLCH scars or usual emphysema due to smoking (Fig. 11). GGOs are a frequent imaging finding and may be associated with the presence of other smoke-related diseases, for example, RB and DIP [6, 7, 24, 29, 30, 33, 38]. Smoking cessation is a fundamental key in the treatment process of PLCH. After smoking cessation, symptoms and radiologic alterations may partially regress or stabilize in more than half of the patients (Fig. 12) [34, 39–46]. However, one third to a half of the patients may show respiratory failure and disease progression, despite smoking cessation (Fig. 13) [47].

PLCH should be differentiated from lymphangioleiomyomatosis (LAM), in which cysts tend to have more regular and rounded shapes and more uniformly distribution through the lung. Other differentials should also be considered, such as pulmonary metastasis, sarcoidosis, Birt-Hogg-Dubé syndrome, and infections (Fig. 14) [32, 35, 48, 49].

Respiratory bronchiolitis and desquamative interstitial pneumonia

RB-ILD and DIP are moderately uncommon diseases related to smoking. On clinical presentation, patients usually
complain about insidious dyspnea and cough over the course of weeks to months \[5–7, 50–54\]. The clinical disease course of RB-ILD and DIP tends to be stable in most of the patients. However, the rates of impairment are worse in those with DIP, in which diffusing capacity for carbon monoxide (DLco) may be severely reduced. As a consequence, deaths can occur in patients with DIP, but there are no described related deaths in those with RB-ILD \[5, 50, 51\]. RB is a classic histological marker of smoking, encountered in the lungs of nearly all active smokers. However, patients with RB are fundamentally asymptomatic, and the disease does not portend any clinical significance. RB and RB-ILD are differentiated by each other by the presence of respiratory symptoms and abnormal pulmonary function tests in the last one \[5–7, 50, 51\].

Histopathologic examinations of RB and DIP show an excess number of pigmented or smokers’ macrophages involving the distal airways and peribronchiolar airspaces. However, DIP presents with pigmented macrophages diffusely filling the alveoli, with associated thickening of the septa secondary to the presence of inflammatory cells. On DIP findings, the degree of interstitial fibrosis is usually mild and more severe than in RB. Both entities represent a severity spectrum of the same pathologic event, with an
excess number of macrophages filling the distal airways and alveoli secondary to an immune-mediated response due to smoking [5, 24, 29, 51, 55, 56].

On imaging, RB/RB-ILD shows upper lung predominance of the findings, characterized by the evidence of low attenuation centriacinar nodules, GGOs, bronchial wall thickening, few thickened interlobular septa, and also lobular air-trapping, especially depicted on expiratory CT. These findings are generally associated with emphysema (Fig. 15). The radiological findings in DIP are lower lobe predominant and characterized by GGOs and reticular opacities interposed with relatively normal lung zones, forming a mosaic attenuation. Small cystic spaces may be depicted in the areas of GGO, representing dilated alveolar ducts or centrilobular emphysema. The distribution of findings is more often subpleural but may also be random or diffuse (Fig. 16) [6, 7, 24, 29, 30, 54, 56]. Associated findings of RB and emphysema are frequently visualized.

Some differential diagnoses are important to be considered in association with patient’s complete clinical history, including NSIP, hypersensitivity pneumonitis, and atypical infections, including pneumocystosis (Figs. 17 and 18) [7, 24, 29, 50].

**Interstitial fibrosis**

**Airspace enlargement with fibrosis/smoking-related interstitial fibrosis**

Cigarette smoke leads to alveolar wall fibrosis that increases with time and intensity of exposure, called AEF, also termed as SRIF. Pulmonary fibrosis severity ranges from sparse fibrosis in the alveolar walls to diffuse fibrosis, with dense, paucicellular, eosinophilic collagen that has a waxy quality on pathologic examination. Hypertrophic smooth muscle bundles can also be depicted and perhaps predominate. AEF is also accompanied by features of emphysema and RB [57–59]. The fibrosis is confined in the subpleural and peribronchiorlar interstitium, with relative preservation of the lung architecture [60]. It is important to mention that AEF is an incidental histologic or radiological finding characterized by interstitial fibrosis exceeding the fine fibrosis often seen in emphysema alone. Most patients have stable disease and good survival time [60, 61]. Therefore, patients with progressively worsening exertional dyspnea and cough might have AEF accompanied by chronic interstitial pneumonia such as UIP or nonspecific interstitial
pneumonia (NSIP). In these cases, lung biopsy is crucial for definitive diagnosis [62].

Radiological features of AEF are subpleural sparing thin-walled cysts (TWCs), associated with reticular and ground-glass opacities. Imaging distinction between the typical honeycombing present in idiopathic pulmonary fibrosis (IPF) and TWCs related to smoking may be confusing. The cysts in AEF appear as thin-walled cysts (less than 1 mm) predominantly distributed in the upper lobes and upper and middle portion of the lower lobes, slightly distant from pleura, affecting deeper lung parenchyma (Fig. 19a) [63–65].

**NSIP/UIP**
The progression of fibrosis leads to increasing lower-lobe predominant GGOs, traction bronchiectasis, and reticulation, in a pattern compatible with NSIP on imaging examination (Fig. 19) [5, 24, 61, 66]. These changes are often accompanied by other smoking-related findings, such as
emphysema, DIP, and RB. In AEF, emphysema may appear better-demarcated secondary to the presence of fibrosis in the alveolar walls [5, 63–65].

IPF is a progressive chronic fibrosing lung disease with unknown etiology and pathologically described by a pattern consistent with UIP [67]. It represents the most common but also the most severe type of ILD, affecting most frequently males over the age of 65 years. The median survival time after the diagnosis ranges from 2 to 4 years. Cigarette smoking is considered a probable risk factor for the development of IPF, with an odds ratio ranging from 1.6 to 2.9 [50, 67–69]. Cigarette smoking is also linked to lower survival time in relation to non-smoker IPF patients [70, 71]. Imaging features are often bilateral and asymmetric and include peripheral and basal predominant traction bronchiectasis, reticular opacities, and honeycombing, with minimal GGOs. Pulmonary volumes are typically low. The findings are spatially and temporally heterogeneous, with areas of varying disease extent and severity adjacent to regions of a more normal lung. The evidence of any of the following features should prompt an alternative diagnosis: fibrosis predominantly located in the upper or mid lungs, extensive GGOs, peribronchovascular distribution, diffuse cysts or nodules, predominant consolidation, and presence of air trapping with substantial mosaic attenuation [72].
**Combined pulmonary fibrosis and emphysema**

The disease termed CPFE is a severe respiratory condition integrating imaging features of both pulmonary fibrosis and emphysema. Patients present with similar symptoms to IPF and emphysema; however, they have relatively preserved spirometry, as a result of the combined obstructive disease in distal airways and restrictive fibrosis. The clue for the diagnosis is the evidence of the physiologic decline in diffusing capacity and characteristic CT features [73–79].

The histological and radiological patterns of interstitial fibrosis described in CPFE are most commonly UIP and, in a minority of reported cases, NSIP [50]. CPFE syndrome is found more frequently in heavy-smoker males and portends a tendency to appear in a slightly older age group in relation to IPF alone (mean age of 65–70 years) [77–79]. CPFE confers a median survival time nearly double that of IPF (approximately 6.1 years) [81]; however, CPFE portends a higher risk of development of pulmonary hypertension (ranging from 50% to 90%) [82, 83] and may also be associated with a greater chance of lung cancer, with consequent lower survival time [84]. Imaging features are emphysema (both CLE and PSE) in the upper lobes associated with interstitial fibrosis in the lower lobes [31, 50, 76–82, 85, 86]. Ryerson et al. [80] reported that CLE should involve a minimum of 10% of the lung volume to allow the diagnosis. Bulky cystic lesions with thick walls predominantly located in the upper lobes are also apparent, which may correspond to emphysema with thick walls predominantly located in the upper lobes [73, 76–82, 85, 86]. Ryerson et al. [80] reported that CLE should involve a minimum of 10% of the lung volume to allow the diagnosis. Bulky cystic lesions with thick walls predominantly located in the upper lobes are also apparent, which may correspond to emphysema with fibrosis or AEF (Fig. 20) [85, 86].

**Conclusion**

Diffuse smoking-related lung diseases exemplify a wide clinicopathologic manifestation secondary to the same process of lung injury. Histologic findings frequently overlap in a single patient and as a consequence mixed patterns of the disease may be depicted on HRCT. The multidisciplinary approach by an integrated clinical, radiological, and pathological study is useful for the best comprehension and distinction of these entities.

**Abbreviations**

AEF: Airspace enlargement with fibrosis; AEP: Acute eosinophilic pneumonia; ALL: Acute lung injury; ARDS: Acute respiratory distress syndrome; BAL: Bronchoalveolar lavage; BMI: Body mass index; CLE: Centrilobular emphysema; COPD: Chronic obstructive pulmonary disease; CPFE: Combined pulmonary fibrosis and emphysema; DIP: Desquamative interstitial pneumonia; DLco: Diffusing capacity for carbon monoxide; GGO: Ground-glass opacity; HRCT: High-resolution computed tomography; ILED: Intestinal lung disease; IPF: Idiopathic pulmonary fibrosis; LAM: Lymphangioleiomyomatosis; NSIP: Nonspecific interstitial pneumonia; PLE: Panlobular emphysema; PSE: Paraepithelial emphysema; RB: Respiratory bronchiolitis; SRIF: Smoking-related interstitial fibrosis; TWC: Thin-walled cyst; UIP: Usual interstitial pneumonia

**Acknowledgements**

None

**Authors’ contributions**

All authors contributed to the collections of cases and development/content of the manuscript. All authors read and approved the final manuscript.

**Funding**

The authors state that this work has received any funding.

**Availability of data and materials**

All data and materials presented were from our hospital and daily practice.

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Competing interests**

The authors declare that they have no competing interests.

**Received:** 7 April 2019 **Accepted:** 2 July 2019

**Published online:** 16 July 2019

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