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Seminars in
ROENTGENOLOGY

Smoking-Related Diffuse Lung Diseases

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Introduction

Cigarette smoking is the leading cause of preventable death in the United States and is the largest risk factor for developing cancer, cardiovascular disease, and chronic obstructive pulmonary disease.[1] Understanding of the association between cigarette smoking and the ensuing complex injury to the lung comes from increased recognition of direct toxicity of cigarette smoke and the resultant tissue responses affecting the airways, alveolar spaces, and alveolar walls. The combination of these sites of injury and associated tissue reactions adversely affect lung mechanics and gas exchange, leading to clinical manifestations including dyspnea, cough, hypercarbia, and hypoxemia.[2,3]

This article focuses on the CT findings of smoking-related diffuse lung injuries including the spectrum of respiratory bronchiolitis (RB), RB-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), pulmonary Langerhans cell histiocytosis (PLCH), acute eosinophilic pneumonia (AEP), and lung fibrosis. While describing each pattern of injury as a separate entity can facilitate understanding of the histopathology and CT manifestations, the reader needs to understand that more often than not a combination of injury patterns is encountered in tissue specimens of smokers, accounting for the wide variety of phenotypes of respiratory disease affecting smokers.

Distribution of Disease

An important facet of smoking-related lung injury is that, for the most part, the upper lobes are affected earlier and more severely. This occurs because the lymphatics of the lower lobes are better developed and are better able to clear inhaled particles and associated inflammatory cells.[4] This phenomenon is not only seen with smoking-related emphysema and smoking-related diffuse lung diseases but also with pneumoconiosis,[5] sarcoidosis,[6] and lung cancer.[7,8]

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While cigarette smoke can injure any part of the lung, early injury and tissue response most commonly occur around the respiratory bronchioles, which are located in the center of the pulmonary lobule. This centrilobular predominant distribution is seen commonly on CT with many smoking-related lung diseases.[2] More confluent abnormalities on CT are associated with more extensive injury and tissue reaction throughout the pulmonary lobules.

Respiratory Bronchiolitis, RB-Associated Interstitial Lung Disease, and Desquamative Interstitial Pneumonia

RB is a nearly universal tissue response to cigarette smoke and is characterized by the accumulation of pigmented macrophages in and around the respiratory bronchioles. These "smokers' macrophages" have a characteristic yellow-brown cytoplasmic pigment resulting from phagocytosis of inhaled cigarette smoke particles and are present on nearly every biopsy specimen from smokers.[9,10] The overwhelming number of patients with RB have no directly related symptoms or altered respiratory function. Thus, RB should be viewed as tissue response to smoking rather than as a distinct disease.

Most patients with histopathologic RB have no related findings on CT.[11] With more extensive RB, poorly-defined centrilobular, upper lobe predominant nodules are visible on CT (Fig. 1). As routine use of thin-section chest CT both for lung cancer screening, nodule characterization, and general chest imaging becomes more commonplace, radiologists will likely encounter findings of RB more frequently. The differential diagnosis for poorly-defined centrilobular nodules also includes active inflammatory hypersensitivity pneumonitis (HP). Because smoking provides some degree of protection against developing HP presumably because of impaired macrophage function, emphysema on CT or a history of cigarette smoking can be helpful in distinguishing RB from HP.[12]

RB-ILD is defined as a clinical-radiologic-pathologic consensus diagnosis.[13] The histopathologic and imaging findings

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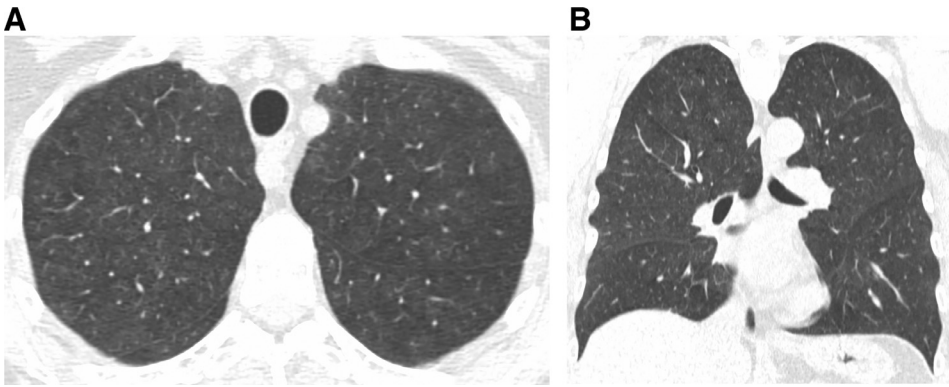

Figure 1 A 42-year-old asymptomatic female smoker with respiratory bronchiolitis. Axial (A) and coronal reformatted (B) CT images show mid and upper lung predominant centrilobular ground-glass nodules.

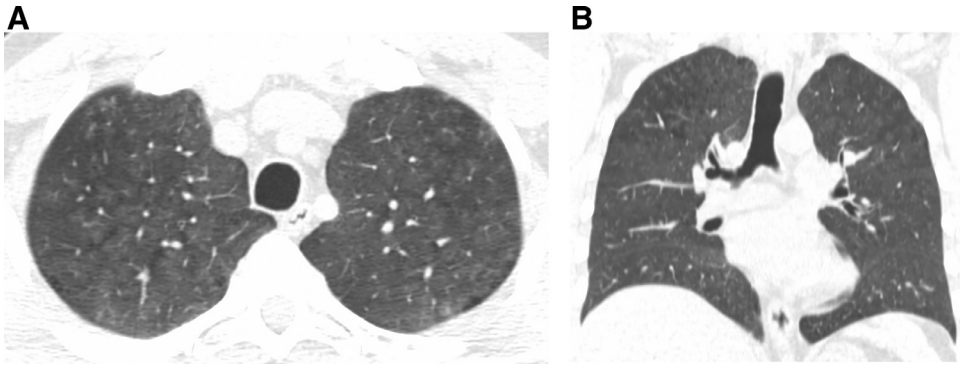

Figure 2 A 35-year-old male smoker with respiratory bronchiolitis-associated interstitial lung disease. Axial (A) and coronal reformatted (B) CT images show extensive mid and upper lung predominant ground-glass opacity. Minimal upper lobe emphysema is present.

of RB and RB-ILD are identical, but patients with RB-ILD have symptoms such as dyspnea and cough and abnormal pulmonary function tests, which cannot be attributed to another cause (Fig. 2). Why only a very small number of smokers develop RB-ILD when nearly all smokers have histopathologic RB remains unclear.

DIP is a misnomer and legacy term carried forward from the original Liebow description of idiopathic interstitial pneumonias.[14] It has been known for some time that the intra-alveolar cells initially thought to be desquamated pneumocytes are actually smokers' macrophages.[13] While DIP is considered to be the part of the spectrum that includes RB and RB-ILD, it is considered a different clinical-radiologic-pathologic consensus diagnosis because not all cases are smoking related.[3,13] Histopathologically, DIP typically is characterized by a more diffuse accumulation of smokers' macrophages throughout the pulmonary lobule and often throughout an entire region of a biopsy specimen.[15] Variability in pathologic descriptions of

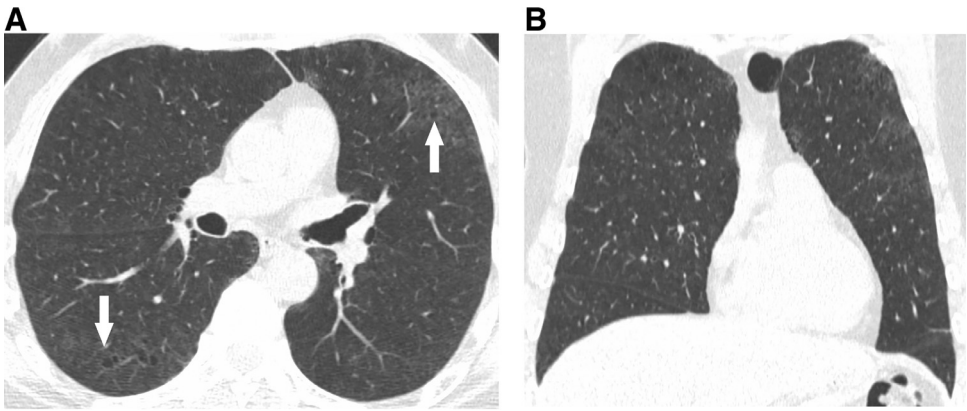

Figure 3 A 52-year-old male smoker with mild desquamative interstitial pneumonia. Axial (A) and coronal reformatted (B) CT images show patchy ground-glass opacity predominantly in the mid and upper lungs. Several small cystic spaces (*arrows*) are located within areas of ground-glass opacity. Mild paraseptal emphysema is also present.

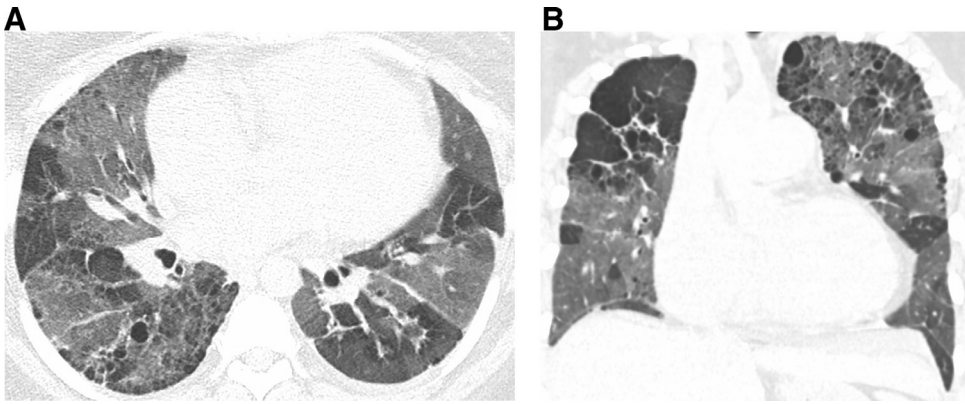

Figure 4 A 45-year-old female heavy smoker with severe desquamative interstitial pneumonia. Axial (A) and coronal reformatted (B) CT images show extensive ground-glass opacity with some lobular sparing. Upper lobe predominant emphysema is present, and there are scattered thin-walled cysts. Case courtesy of Arlene Sirajuddin, M.D. (Bethesda, MD).

DIP can result from subjective differences in biopsy interpretation and is impacted by biopsy site(s).[16]

The typical CT findings of DIP are patchy ground-glass opacity and adjacent areas of normal lung (Figs. 3 and 4). The more extensive ground-glass opacity on CT reflects the more profuse accumulation of smokers' macrophages throughout the lobule and region of lung. In contrast to RB/RB-ILD and other inhalational lung diseases, DIP is usually basal predominant, the reason for which is unclear.[17-19] Many patients also have poorly-defined centrilobular nodules in the upper lungs (reflecting RB) and emphysema. One helpful CT finding in DIP is the presence of small cystic spaces within the areas of ground-glass opacity. It is uncertain if these lucent spaces are true cysts or small foci of emphysema.[2] Patients with DIP can also have findings of fibrosis such as fine reticulation and architectural distortion.[20]

Pulmonary Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is part of a group of distinct systemic diseases called the histiocytoses. PLCH is subtype of LCH that is limited to the lungs and is considered a smoking related diffuse lung disease in over 90% of patients.[3] Langerhans cells are subset of antigen-presenting dendritic cells that reside in the tracheobronchial mucosa and only a few other organs. Cigarette smoking causes an increase in the number of Langerhans cells in the lungs.[21] The cause of this increase is unknown but is believed to be a response to the antigens and inflammation that occur from smoking. As with RB-ILD, only a small number (<4%) of smokers develop PLCH,[22] suggesting a component of genetic predisposition. Mutations in v-Raf murine sarcoma viral oncogene homolog B (BRAF), v-Raf murine sarcoma 3611 viral oncogene homolog (ARAF), and mitogen-activated protein kinase 1 (MAP2K1) have been detected in patients with both systemic LCH and PLCH.[23] In contrast to systemic forms of LCH where a monoclonal proliferation is typical, PLCH is believed to be a polyclonal proliferation in smokers.[24,25]

Cigarette smoking and less commonly exposure to second-hand cigarette smoke is the single largest risk factor for developing PLCH.[21,26] PLCH can occur at any age, but most patients are 20-40 years of age at presentation with equal sex distribution.[27] PLCH is reported to occur most often in Caucasians.[28] Approximately 75% of patients are asymptomatic at diagnosis, likely reflecting the increased use of chest CT for vague chest symptoms. Symptoms of PLCH overlap with those of other diffuse lung diseases and include cough and shortness of breath. Up to one-third of patients can develop constitutional signs and symptoms such as weight loss, night sweats, and fever, similar to lymphoma and chronic infection.[26] Pneumothorax is reported to occur in up to 15% of patients and may be the presenting finding.[29] Pulmonary hypertension can develop in patients with PLCH, particularly those with more advanced disease, and is an independent predictor of increased mortality.[3,30,31]

Early in the course of PLCH, Langerhans cells and other inflammatory cells coalesce around the bronchioles forming characteristic inflammatory nodules. With time, central cavitation develops as the bronchiole wall is damaged and the small airway dilates. Cavitary nodules can coalesce forming cysts, which can take on bizarre shapes. Fibrous tissue forms around the cavity. More advanced lesions may consist purely of fibrous tissue with no remaining Langerhans cells. This scarring can cause paracicatricial airspace enlargement.[2]

As with histopathology, the CT findings of PLCH vary on the stage and extent of the disease. Early in the disease course, small (<10 mm) well defined, stellate centrilobular nodules may be present, predominantly in the mid and upper lung zones (Fig. 5). Central lucency develops with early cavitation, and the nodules eventually form small cysts (Fig. 6).[29] Progressive expansion and coalescence of cysts leads to formation of larger, irregular cysts. Late in the course of the disease, fibrosis surrounding the cavity increases, and paracicatricial air space expansion ensues.[2] Advanced PLCH can be mistaken for severe emphysema on CT (Fig. 7).[28] However, in this author's experience, the underlying pulmonary vasculature is typically better preserved with PLCH

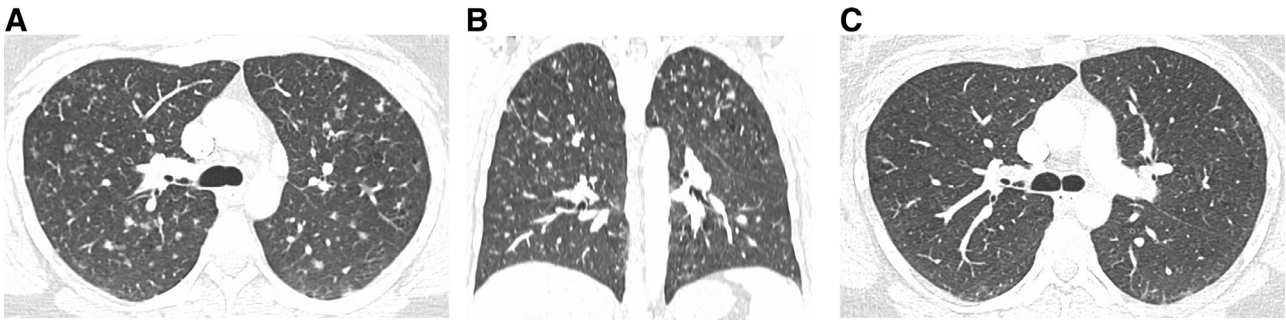

Figure 5 A 38-year-female smoker with pulmonary Langerhans cell histiocytosis. Axial (A) and coronal reformatted (B) CT images show upper lobe predominant stellate nodules (*arrows*) and mild centrilobular emphysema. CT image 9 months after smoking cessation (C) shows resolution of the nodules.

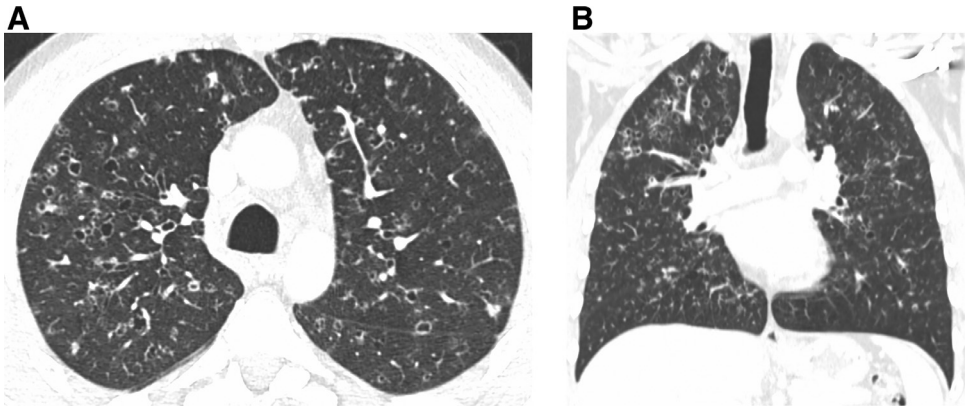

Figure 6 A 44-year-old male smoker with pulmonary Langerhans cell histiocytosis. Axial (A) and coronal reformatted (B) CT images show upper lobe predominant nodule and irregular cysts. Note the conspicuous sparing of the costophrenic sulci.

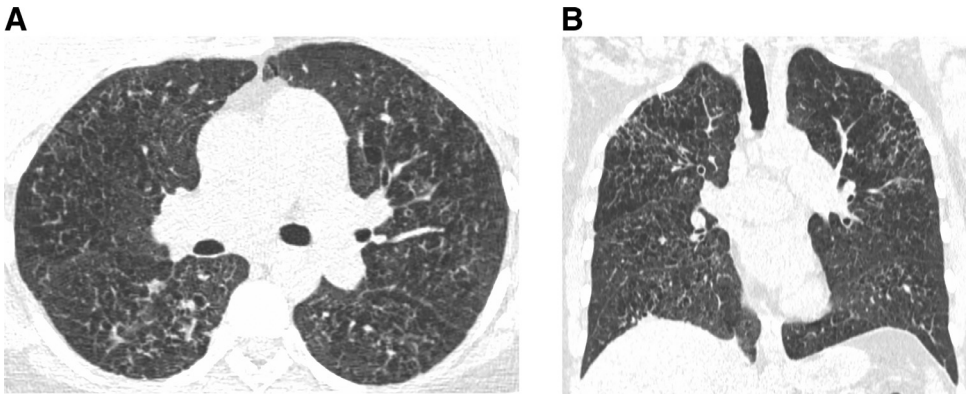

Figure 7 A 54-year-old female smoker with end-stage pulmonary Langerhans cell histiocytosis and pulmonary hypertension. Axial (A) and coronal reformatted (B) CT images show confluent upper lung predominant cysts mimicking emphysema. Central pulmonary arteries are enlarged. Note conspicuous sparing of the costophrenic sulci.

than with emphysema. Because patients with PLCH can develop pulmonary hypertension, the pulmonary arteries may become enlarged, and the right ventricle can dilate and hypertrophy.

Smoking cessation is the main treatment for PLCH. The majority of patients will have improved or stable disease with or without smoking cessation.[28,32] Patients with refractory disease may be treated with corticosteroids, immunosuppression, or chemotherapy, although no large scale randomized control trials addressing effectiveness have been performed.[3]

Acute Eosinophilic Pneumonia

AEP is an acute lung injury characterized by accumulation of eosinophils in the lung interstitium and alveoli resulting

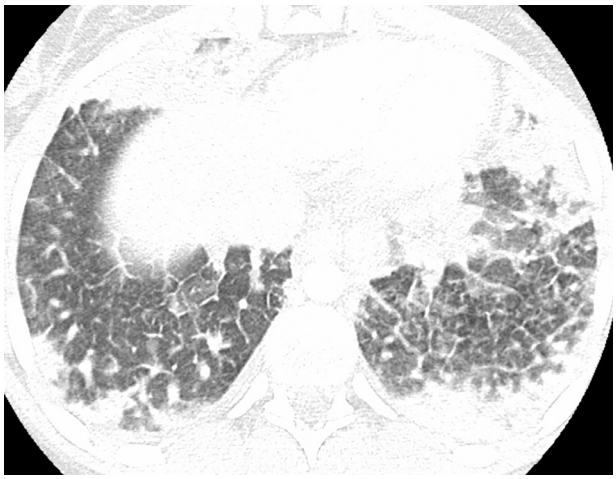

Figure 8 A 18-year-old female with acute respiratory distress and acute eosinophilic pneumonia related to new onset smoking. Unenhanced CT image shows smooth septal thickening and subpleural predominant ground-glass opacity and consolidation. The patient made a full and prompt recovery following therapy with corticosteroids.

in injury to the basement membrane between the capillary endothelium and alveolar epithelium. The ensuing leakage of blood and other substances in the air spaces leads to diffuse alveolar damage.[33] Causes of AEP include drug reaction, infection, and immunologic diseases.[34] Cigarette smoking is also a known cause of AEP, although the mechanism is unclear. Smoking-related AEP almost always occurs in new smokers, former smokers who resume smoking, and smokers who increase the amount of smoking.[35-37] Patients with smoking related AEP tend to have a more severe clinical presentation than those with AEP from other causes.[38]

The CT findings of AEP are similar to other acute lung injuries and include consolidation and ground-glass opacity. Septal thickening and small pleural effusions are also common. The distribution of findings is typically diffuse or basal predominant (Fig. 8).[39,40]

Patients present with fever, hypoxemia, and dyspnea. Many require mechanical ventilatory support.[3,41] The diagnosis of AEP is usually established on bronchoalveolar lavage, as the majority of patients lack blood eosinophilia, and CT findings are similar to other acute lung injuries.[42] Marked improvement occurs quickly after starting treatment with corticosteroids.[43]

Fibrosis

The link between cigarette smoking and lung fibrosis has gained recent attention and has been referred to by a variety of terms including RB-ILD with fibrosis, smoking-related interstitial fibrosis, and airspace enlargement with fibrosis.[44] The presence of alveolar wall fibrosis was described in detail in 1963 by Auerbach et al.[45] Much of the variation in nomenclature probably reflects the broad range of histopathologic findings encountered on biopsy, lobectomy, and explant specimens. Some patients may have small foci of alveolar wall fibrosis on biopsy whereas other may have diffuse alveolar wall fibrosis in a nonspecific interstitial pneumonia pattern. Rather than distinct diseases, these different terms reflect the spectrum of smoking-induced airway wall fibrosis.[44] Furthermore, the link between smoking and idiopathic pulmonary fibrosis is well established with the majority of patients with idiopathic pulmonary fibrosis having a smoking history.[46,47]

Combined pulmonary fibrosis with emphysema (CPFE) has been described as a distinct clinicopathologic entity.[48] However, given the common exposure of cigarette smoke and the ensuing direct and indirect injuries to the lung, it is not surprising that emphysema, airway injury, and fibrosis are all encountered in varying degrees of severity in some smokers. Patients with CPFE may have severe dyspnea despite normal or near normal spirometry, the latter a reflection of the combination of restrictive physiology related to fibrosis and obstruction from small airways disease. In contrast to spirometry, the diffuse capacity (DL_{CO}) is typically quite low.[49] Patients with CPFE also are reported to have higher rates of pulmonary hypertension and lung cancer.[49,50] CT shows a variable degree of smoking-related emphysema and findings of fibrosis (Fig. 9).

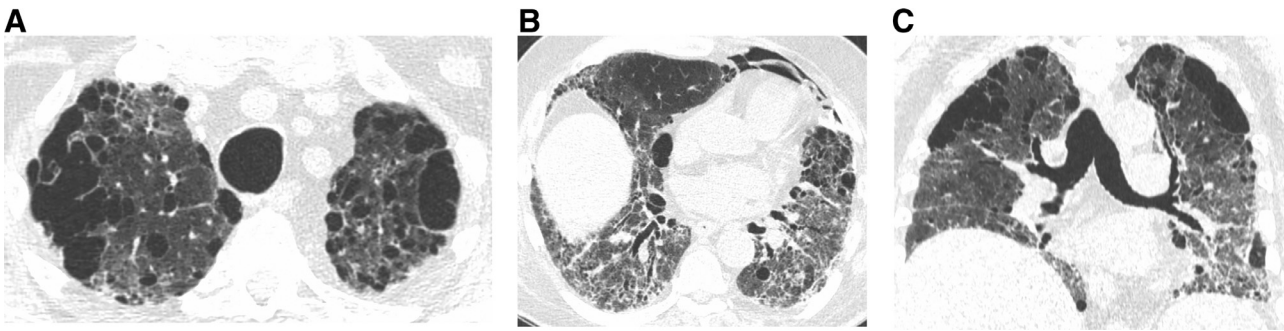

Figure 9 A 72-year-old male smoker with combined pulmonary fibrosis and emphysema. Axial (A-B) and coronal reformatted (C) unenhanced CT images show upper lobe predominant emphysema with large bullae and basal predominant fibrosis characterized by reticulation and traction bronchiectasis. Spontaneous pneumomediastinum (*arrow*) had developed without acute symptoms.

Conclusion

While specific clinical-radiologic-pathologic consensus diagnoses and specific smoking-related lung diseases are frequently presented as distinct entities, it is important to recognize that the broad range of clinical, radiologic, and histopathologic manifestations of smoking-related diffuse lung diseases occurs because of the coexistence and variability of direct toxicity of cigarette smoke on the lung and subsequent tissue responses. The radiologist will be confronted with a variety of patterns on CT scans of current and former smokers including emphysema, ground-glass opacity, small nodules, cysts, and reticulation. Recognizing that all of these findings can be the result of smoking can help the radiologist suggest that combination of abnormalities can all be attributed to cigarette smoke exposure and could explain the patient's signs and symptoms.

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