

Smoking-related Lung Disease

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Abstract: Dyspneic smokers who come to clinical attention demonstrate varying combinations of emphysema, airway inflammation, and fibrosis in addition to the changes of pulmonary Langerhans' cell histiocytosis. There is also growing acceptance of a link between cigarette smoke and alveolar wall fibrosis. Acute eosinophilic pneumonia is a dramatic response to recent-onset smoking seen in a small number of individuals. The interconnected pathways that lead to lung inflammation and fibrosis in cigarette smokers are slowly coming into focus.

Key Words: cigarette smoke, macrophage, respiratory bronchiolitis, desquamative interstitial pneumonia, fibrosis, Langerhans' cell, acute eosinophilic pneumonia, emphysema

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Inhalation of cigarette smoke is tacitly accepted as the main cause of chronic obstructive pulmonary disease and is characterized by airflow limitation that is not fully reversible and is commonly progressive.¹ Cigarette smoke is a powerful inducer of inflammation that is primarily orchestrated by increased numbers of macrophages that are attracted and retained in the lung.^{2,3} These macrophages draw additional inflammatory cells into the lung including neutrophils, monocytes, eosinophils, and T-lymphocytes. The result is a destructive cascade of elastolytic compounds and reactive oxidative species that destroy the lung structure resulting in emphysema and obstructive bronchiolitis (Figs. 1, 2). Langerhans' cells, a subtype of dendritic cells, form a rich network on the surface of airways. They increase in number with exposure to the cigarette smoke, accelerating airway inflammation and dysfunction, often resulting in bronchiolocentric stellate nodules and scars.²

Intimately coupled to this destructive inflammatory cascade is a distorted attempt at lung and airway repair, which is observed microscopically, as deposition of the collagen and fibrous tissue.⁴ Bronchiolar fibrosis is the primary driver of small airway obstruction in chronic

obstructive pulmonary disease and is strongly associated with progressive disease.⁵ This form of fibrosis is associated with the intensity and duration of cigarette smoke exposure.^{6,7} Alveolar wall fibrosis is also commonly observed in cigarette smokers. A substantial literature documents the association between cigarette smoke and alveolar wall fibrosis^{4,8–17} and there is increasing recognition of the syndrome of combined pulmonary fibrosis and emphysema that is distinct from idiopathic pulmonary fibrosis.^{18–21}

We have traditionally attempted to subclassify the smoking-related lung injury by the predominant cell type and distribution within the lung parenchyma. The result is a list of legacy terms, some of which have been carried forward over decades, despite substantial changes in our understanding of the underlying pathophysiology.^{22,23} The list includes:

- Emphysema
- Obstructive bronchiolitis
- Respiratory bronchiolitis-interstitial lung disease (RB-ILD)
- Desquamative interstitial pneumonia (DIP)
- Pulmonary Langerhans' cell histiocytosis (PLCH)
- Acute eosinophilic pneumonia (AEP).

The above categories, although compelling in their seeming utility, obscure the growing realization that variable combinations of inflammatory cells and fibrosis are commonly identified in most cigarette smokers who come to open lung biopsy. Greater progress in understanding the human response to cigarette smoke may come from investigating what binds these process together rather than drawing lines between them. In the meantime, we have described the diseases according to currently accepted categories while highlighting the overlap between processes where appropriate.

RB AND RB-ILD

In 1974, Niewoehner described the presence of pigmented macrophages in and around the respiratory bronchioles of young smokers and postulated that these macrophages were the precursor of centrilobular emphysema.²⁴ More recent longitudinal imaging studies lend support to the concept that the macrophages of respiratory bronchiolitis (RB) play an important role in alveolar wall destruction.²⁵ The presence of pigmented macrophages in the lung is a highly accurate marker for cigarette smoking with most of the RB patients reporting either current or past cigarette use.⁷ The macrophages can persist for decades after individuals have stopped smoking.^{7,26} The majority of patients with RB are asymptomatic, however, as reported by Myers et al²⁷ some patients present with nonspecific symptoms including dyspnea and cough. Most are heavy smokers with restrictive or mixed restrictive/obstructive pulmonary functions that suggest the presence of interstitial lung disease.²⁶ These patients now carry the diagnosis of RB-ILD, a term conceived by Yousem et al.²⁸

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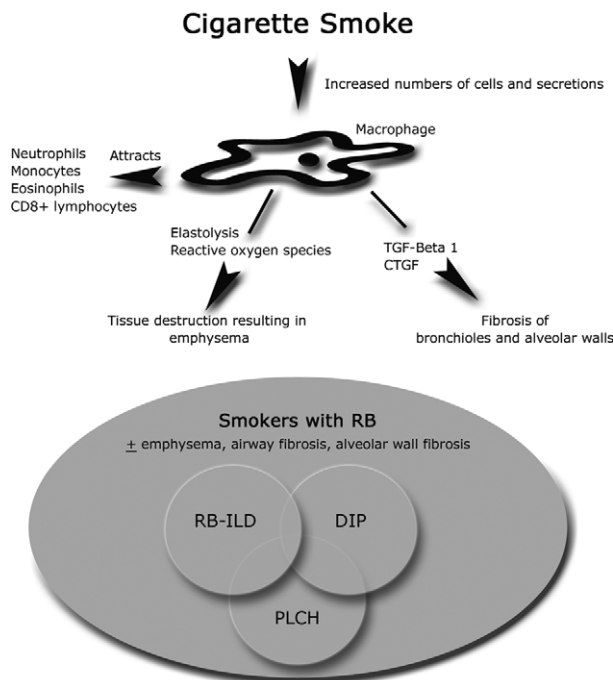


FIGURE 1. Cigarette smoke injury. Cigarette smoke attracts and activates the macrophages leading to a cascade of inflammatory, oxidative, and profibrotic substances within the lung. The result is varying combinations of accumulated inflammatory cells, emphysema, peribronchiolar, and alveolar wall fibrosis. On the basis of the predominant pathophysiology a number of clinical diagnoses are in current use including: RB, RB-ILD, DIP, and PLCH. CTGF indicates connective tissue growth factor; DIP, desquamative interstitial pneumonia; TGF, transforming growth factor. Modified from *Eur Respir J.* 2003;22:672–688; *Chest.* 2003;124:1199–1205.

HISTOPATHOLOGIC FINDINGS

RB is a histopathologic lesion. It is the most common form of small airways injury and is seen virtually in all biopsy specimens from cigarette smokers.⁷ RB is characterized by airway-centered accumulations of macrophages containing finely granular yellow-brown cytoplasmic pigment within distal bronchioles, alveolar ducts, and adjacent alveolar spaces (Fig. 2C). Cytoplasmic pigmentation is variable and correlates with the number of pack-years smoked.⁷ The macrophages may be accompanied by mild chronic interstitial inflammation (Fig. 2D), and/or mild fibrosis of the airway and peribronchiolar alveolar septa (Fig. 2E). There are no histologic features that separate RB and RB-ILD. RB-ILD, which is rare, is a clinical-radiologic-pathologic diagnosis defined by pulmonary symptoms, abnormal pulmonary functions, abnormal imaging, and a surgical lung biopsy demonstrating RB.⁷

RADIOLOGIC FINDINGS

In a large prospective study, asymptomatic smokers demonstrated upper lobe predominant parenchymal abnormalities including micronodules (27%), areas of ground-glass (21%), emphysema (21%), and bronchial wall thickening (33%).²⁹ Histologic correlation found changes of RB and thickening of alveolar walls with inflammatory cells in areas of ground-glass with bronchiolectasis and peribronchiolar

fibrosis in area of micronodularity (Fig. 3).³⁰ Similar results have been found in a more recent study of patients with RB-ILD in which the most common findings included: bronchial wall thickening, centrilobular nodules, areas of ground-glass, and upper lobe predominant centrilobular emphysema (Fig. 3).³¹ Areas of hypoattenuation were noted in 38% and were most likely related to air trapping. In addition to RB the differential for micronodules in smokers (Fig. 4) encompasses PLCH, bronchiolar fibrosis, and the premalignant lesion of atypical adenomatous hyperplasia. In nonsmokers the differential for centrilobular nodules and focal areas of low attenuation must include subacute hypersensitivity pneumonitis.³² The likelihood of acquiring hypersensitivity pneumonitis is decreased in cigarette smokers for reasons that are not well understood.

DIP

Averill Leibow described dyspneic patients with numerous inflammatory cells that expanded the alveolar spaces.²³ These cells were originally described as desquamated pneumocytes but are now recognized as alveolar macrophages, the same as those identified in patients with RB and RB-ILD. Given this understanding, there have been calls to change the name to alveolar macrophage pneumonia, however, the use of DIP persists.²² The majority of patients with DIP are cigarette smokers who present with dyspnea, cough, and restrictive pulmonary functions. The clinical phenotype and histology are similar to RB-ILD and it is therefore reasonable to view the 2 diseases as a spectrum of injury in cigarette smokers. However, the incidence of smoking is lower in DIP patients (60% to 90% in reported series) although it is nearly universal in RB/RB-ILD.^{7,33–35} DIP-like reactions have been described in pneumoconioses and drug reactions supporting the need for a category separate from RB/RB-ILD in nonsmokers.²²

HISTOPATHOLOGIC FINDINGS

DIP is characterized by the presence of pigmented macrophages diffusely distributed within alveolar spaces. Although the alveolar walls are variably thickened by diffuse fibrosis and mild infiltrates of chronic inflammatory cells, the alveolar wall architecture is preserved and typically lacks honeycombing. Histologically, the findings in DIP overlap those of RB-ILD and separation of the 2 is based on the distribution of pigmented macrophages. In DIP, macrophages are diffusely distributed throughout the secondary lobule whereas in RB-ILD they are bronchiolocentric. However, macrophage distribution can vary considerably from 1 alveolus to the next and 1 histologic section to another making the separation of DIP from RB-ILD difficult and often quite arbitrary. Assessment of macrophage distribution can be limited by sample size and site biopsied (Fig. 5).

RADIOLOGIC FINDINGS

Homogenous or patchy increase in lung attenuation or ground-glass is reported as the most common finding in patients with DIP in most series.^{33–37} The mid and lower lung zones are predominantly involved (Fig. 5) and there is a predilection for the involvement of the periphery of the lung.³⁴

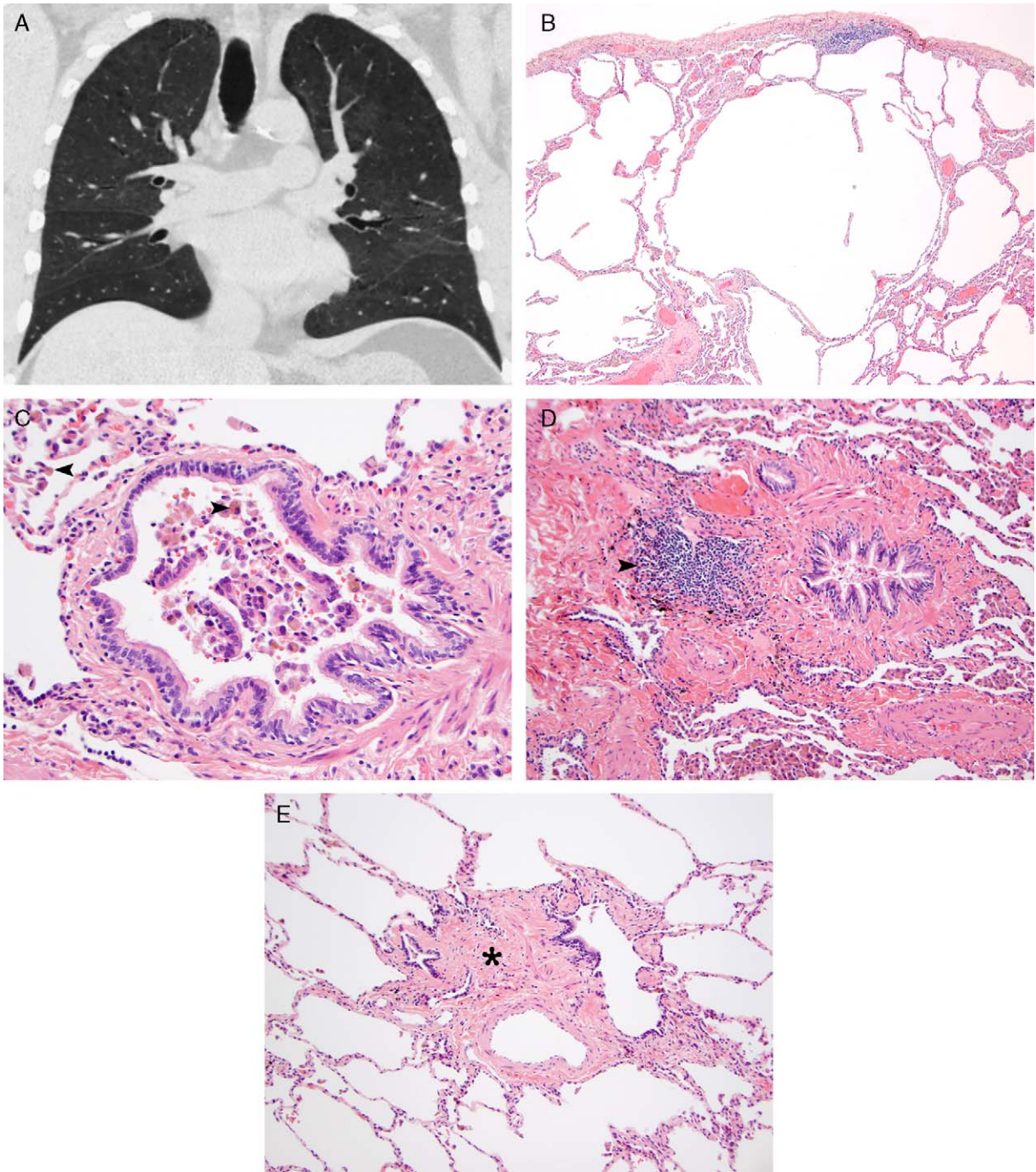


FIGURE 2. Typical spectrum of smoking-related lung injury. A, Coronal computed tomography acquired from axial data demonstrates focal areas of low attenuation consistent with emphysema and geographic areas of ground-glass. B, Emphysema, abnormally large airspaces, is the result of destruction of alveolar walls (hematoxylin and eosin, 100 \times). Airway injury below the level of computed tomography resolution is evidenced by C, respiratory bronchiolitis, so-called "smokers' macrophages" (arrowheads) (hematoxylin and eosin, 200 \times); D, airway-centered chronic interstitial inflammation (arrowhead) (hematoxylin and eosin, 100 \times); and E, bronchiolar fibrosis (asterisk) with airway distortion (hematoxylin and eosin, 100 \times).

CIGARETTE SMOKE AND PULMONARY FIBROSIS

A more contentious issue relates to the acceptance of fibrosis as a part of the expected array findings in cigarette smokers. Niewoehner's seminal description of RB did not

include alveolar wall fibrosis, however, the mean age of his subjects was 25 years.²⁴ Subsequent studies have shown a strong association between bronchiolar fibrosis and the duration of cigarette smoke exposure in older adults.^{6,7}

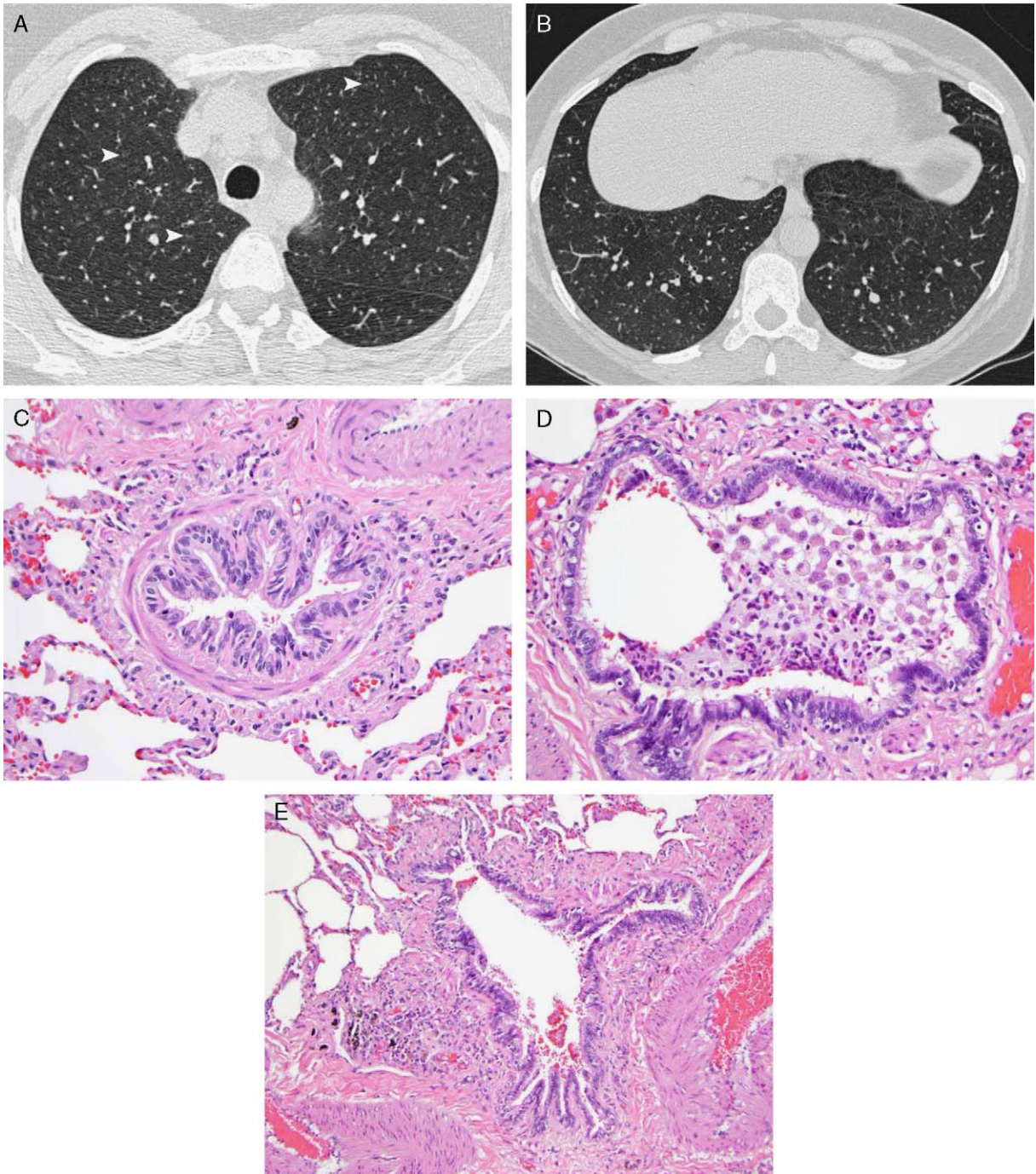


FIGURE 3. Findings in respiratory bronchiolitis. A, Axial computed tomography through the upper lobes demonstrates subtle ground-glass nodules (arrowheads). B, Axial computed tomography through the lower lobes demonstrates subtle mosaic attenuation and minimal airway wall thickening. These computed tomography findings are the result of variable airway involvement ranging from C, normal airways (hematoxylin and eosin, 200 ×) to airways with D, respiratory bronchiolitis (hematoxylin and eosin, 200 ×) and E, bronchiolar fibrosis (hematoxylin and eosin, 100 ×).

Yousem³⁸ recently described 9 patients with RB and diffuse alveolar wall fibrosis that fits the pattern of nonspecific interstitial pneumonia (NSIP).

In Liebow’s original description of DIP, fibrosis of alveolar walls was observed to a “modest degree” and there has been reluctance to accept more severe fibrosis

as a part of the expected range of findings.²³ The current consensus classification does not include fibrosis in its histologic description even though most of the series demonstrate histologic or radiologic evidence of fibrosis in greater than 50% of cases.^{33–36,39} In some cases the fibrosis is relatively uniform and below the resolution of

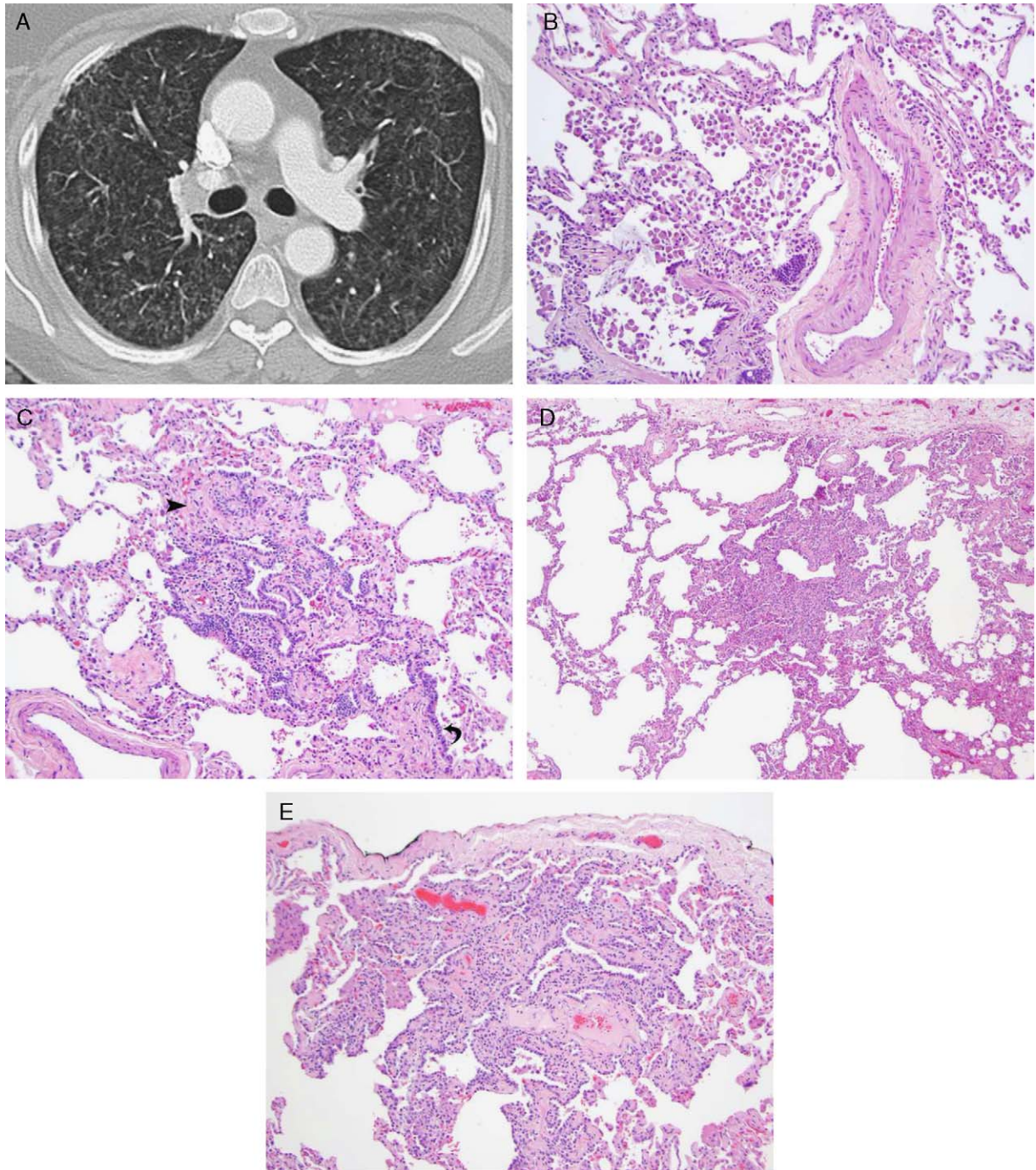


FIGURE 4. Histologic correlates of ground-glass nodules in cigarette smokers. A, Axial computed tomography acquired at the level of the carina demonstrates numerous, ill-defined subcentimeter nodules. A spectrum of pathology underlies the nodules found on imaging including: B, respiratory bronchiolitis (hematoxylin and eosin, 100 \times); C, bronchiolar fibrosis (arrowhead) with peribronchiolar metaplasia (curved arrow) (hematoxylin and eosin, 100 \times); D, pulmonary Langerhans' cell histiocytosis (hematoxylin and eosin, 40 \times); and E, atypical adenomatous hyperplasia (hematoxylin and eosin, 100 \times).

chest computed tomography (Fig. 6). However, in our experience, well-formed cystic spaces, seen on high-resolution computed tomography, that follow the distribution of smoking-related emphysema are common in dyspneic smokers who come to open lung biopsy (unpublished data) (Fig. 7). Those cystic spaces correlate with fibrotic

walls that surround simplified areas of emphysema. The spaces are commonly filled with smoker's macrophages. The fibrosis fits the definition of NSIP.²¹ The well-outlined cystic spaces suggest the possibility of usual interstitial pneumonia, however, the distribution of cysts in this subset of cigarette smokers follows the distribution of

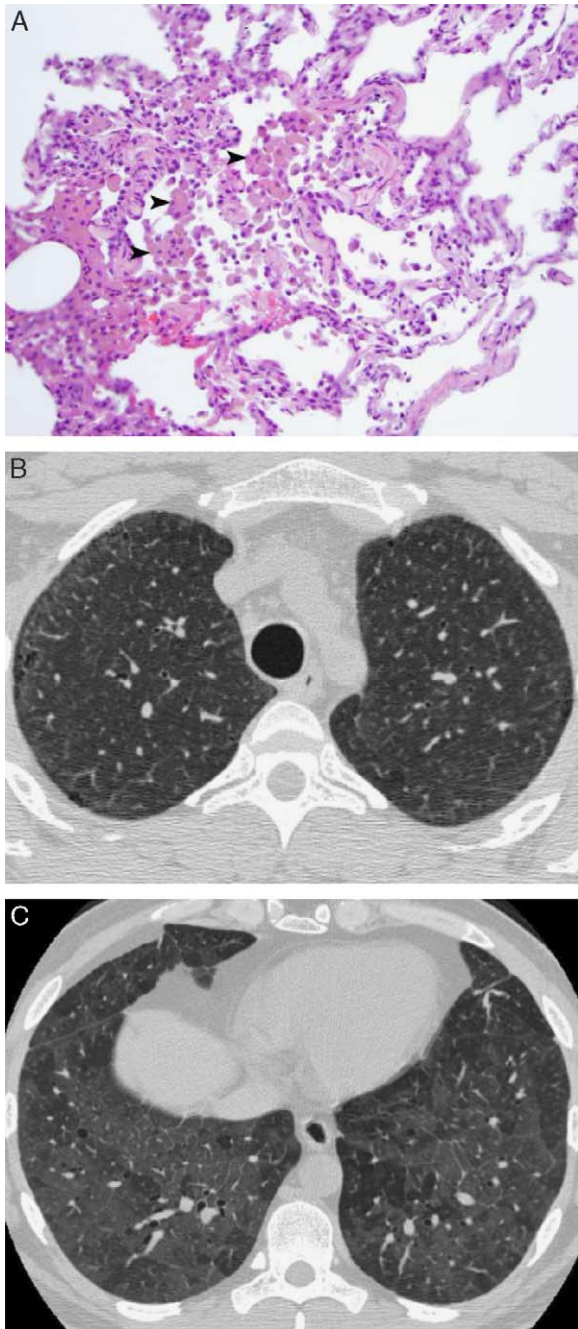


FIGURE 5. Spectrum of respiratory bronchiolitis and desquamative interstitial pneumonia. A, Representative section from a multiple site transbronchial biopsy shows intra-alveolar smokers' macrophages (arrowheads) (hematoxylin and eosin, 200 ×). B, Axial computed tomography through the upper lobes demonstrates the subcentimeter ground-glass nodules, whereas in C, the axial computed tomography through the lower lung fields demonstrates widespread geographic areas of ground-glass. These 2 levels of imaging highlight the variable distribution of airspace macrophage accumulation that can occur in the spectrum of respiratory bronchiolitis/desquamative interstitial pneumonia.

typical smoking-related emphysema. The holes are larger and more prominent in the upper lung fields, which is distinct from usual interstitial pneumonitis in which the

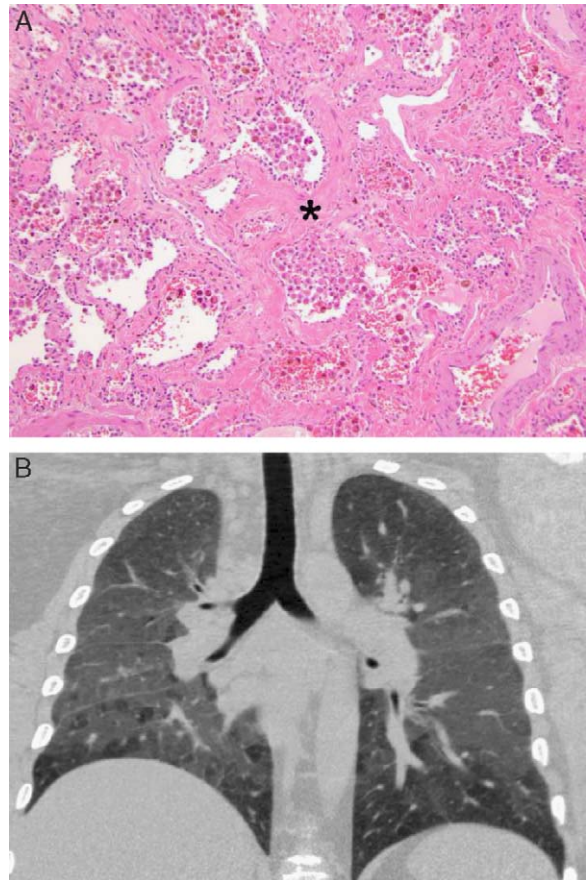


FIGURE 6. Desquamative interstitial pneumonia and fibrosis. A, The diffuse distribution of smokers' macrophages in desquamative interstitial pneumonia is associated with varying amounts of alveolar wall fibrosis (asterisk) (hematoxylin and eosin, 100 ×) that correlates with B, coronal reconstruction of axial computed tomography data demonstrating the diffuse ground-glass attenuation with relative sparing of the bases.

cysts are strikingly peripheral with a lower lobe predominance. Patients who present with combined emphysema and fibrotic NSIP are severely dyspneic with relatively normal spirometry and markedly reduced diffusing capacity of the lung of carbonmonoxide (unpublished data) fit the increasingly recognized syndrome of combined pulmonary fibrosis and emphysema.^{18-21,39} As previously mentioned, there is long standing support for the concept of smoking-related fibrosis other than usual interstitial pneumonitis.^{4,8,9,11,12,14,16,17,38} Hansell and Nicholson speculate that some smokers with the NSIP pattern of fibrosis may represent the late stage of fibrotic DIP in which the macrophages have been cleared from the alveoli.³⁹

PLCH

PLCH is a part of spectrum of disease now collectively known as Langerhans' cell histiocytosis. The classification has been simplified and is based on the presence of single or multiorgan involvement.^{40,41} In the majority of patients PLCH is isolated to the lungs with only 5% to 15%

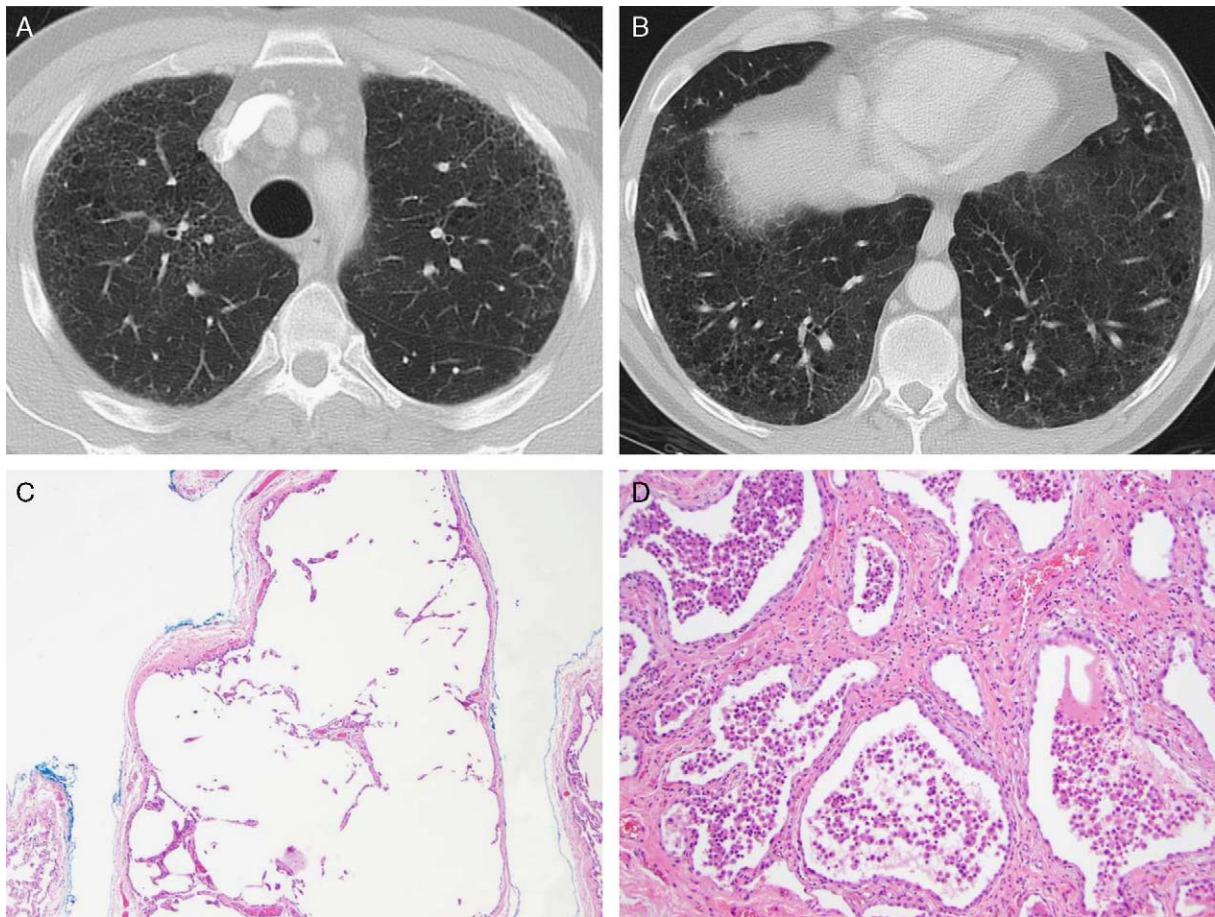


FIGURE 7. Combined pulmonary fibrosis and emphysema is increasingly recognized in older smokers. Axial computed tomography sections through the A, upper and B, lower lobes demonstrate areas of low attenuation that are variably outlined with walls and follow the typical distribution of smoking-related emphysema. Histologic sections show the enlarged and simplified airspaces typical of emphysema; C, without significant alveolar wall fibrosis (hematoxylin and eosin, 40 ×) and, D, associated with alveolar wall fibrosis and airspace accumulation of smokers' macrophages (hematoxylin and eosin, 100 ×).

demonstrating multiorgan involvement including bone lesions, skin lesions, and diabetes insipidus.⁴¹ Patients most commonly present with dyspnea and cough, although up to 25% are asymptomatic at the time of disease discovery. PLCH primarily affects individuals in the 3rd to 5th decade of life, however, the relative frequency of males and females affected remains unsettled with studies demonstrating a slight predominance of either sex.^{42,43} It is an uncommon disease found in approximately 3.4% of patients undergoing open lung biopsy for chronic interstitial lung disease.⁴⁴ The pathogenesis remains unknown, however, 90% or more of PLCH patients are cigarette smokers.^{43,45} Pulmonary hypertension is more prominent in advanced PLCH than in other chronic lung diseases owing to direct intrinsic pulmonary vascular involvement.⁴⁶

HISTOPATHOLOGIC FINDINGS

PLCH is characterized by discrete bronchiolocentric, stellate interstitial nodules (Fig. 8C) which in the early stage are cellular and comprised of Langerhans' cells admixed with

variable numbers of lymphocytes, fibroblasts, eosinophils, neutrophils, plasma cells, and pigmented macrophages (Fig. 8C). Langerhans' cells display characteristic deeply grooved nuclei and are immunoreactive with CD1a and S-100. Over time, early cellular nodules are replaced in a centripetal fashion by fibrous tissue to form cellular and fibrotic nodules and, in the late stage, entirely fibrotic bronchiolocentric stellate scars surrounded by distorted and enlarged air spaces.^{43,47}

RADIOLOGIC FINDINGS

The chest radiograph is usually abnormal demonstrating a mixture of reticular and micronodular opacities predominantly in the mid and upper lung zones (Fig. 8A).⁴⁸ Lung volumes are normal or increased.

High-resolution computed tomography mirrors the typical upper lobe predominance noted on chest radiography but resolves the reticular change into a combination of nodules and cysts with varying wall thickness (Fig. 8B).⁴⁹ The combination of irregularly shaped cysts and peribronchiolar nodules that predominate

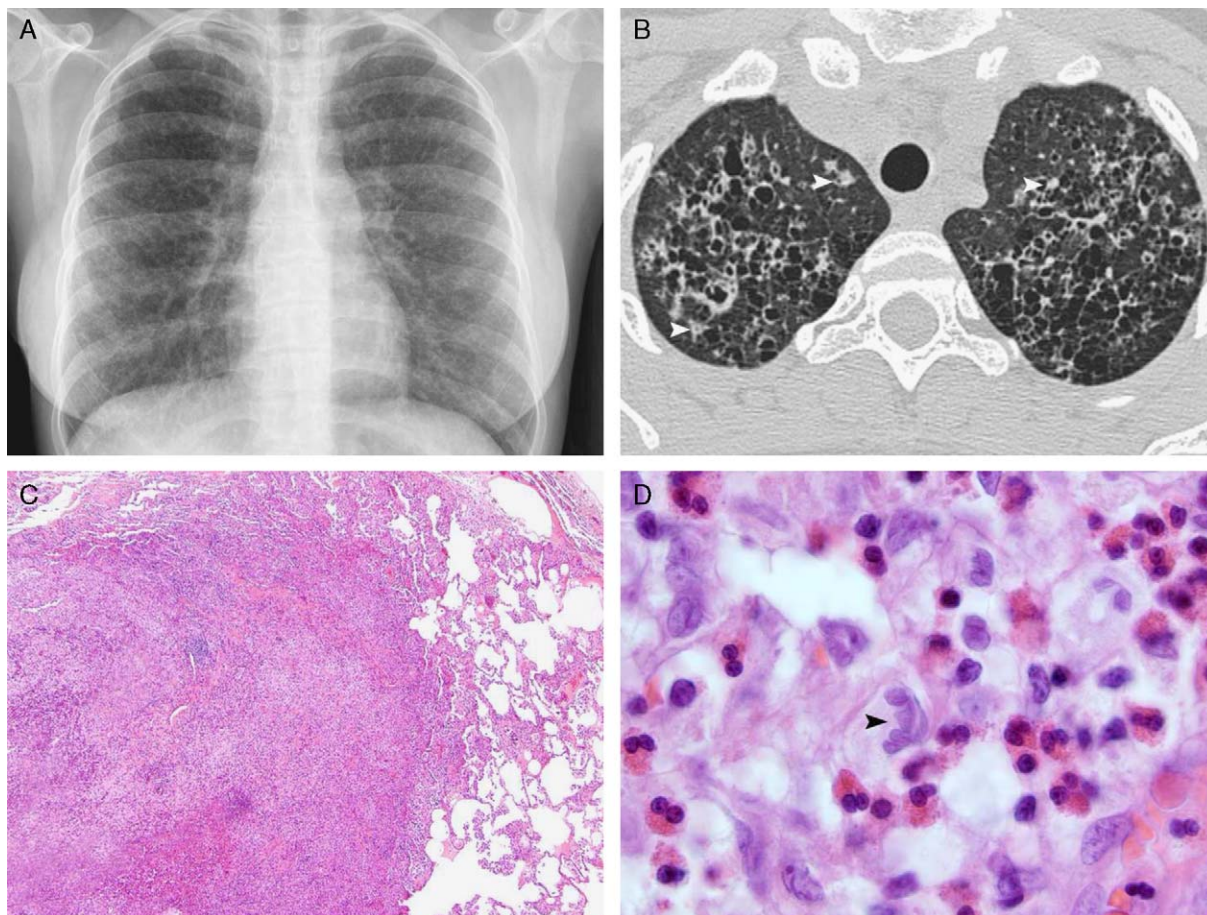


FIGURE 8. Typical findings in early stage pulmonary Langerhans' cell histiocytosis. A, Posteroanterior radiograph demonstrates hyperinflation with reticulation. B, Axial computed tomography through the upper lobes demonstrates a combination of cysts and nodules (arrowheads). C, Histologically the nodules are irregular, stellate, bronchiolocentric interstitial collections of cells (hematoxylin and eosin, 40 \times) including, D, typical grooved Langerhans' cells (arrowhead), eosinophils, neutrophils, and lymphocytes (hematoxylin and eosin, 1000 \times).

in the upper portion of the chest obviates the need for lung biopsy in the appropriate clinical circumstance.⁴¹ Progression from a nodular pattern to a predominance of thin-walled cysts is typical (Fig. 9).⁵⁰ The later stages of the disease are associated with significant emphysema either related to the stellate scarring of PLCH and/or typical smoking-related emphysema (Fig. 10).

Ground-glass attenuation in patients with PLCH correlates with the presence of RB-DIP-like changes highlighting the concept that PLCH, RB, and DIP form a spectrum of injury in cigarette smokers.⁵¹

AEP

AEP was described by Allen et al⁵² and is characterized by an acute febrile illness, hypoxemia, diffuse pulmonary infiltrates, and increased numbers of eosinophils on bronchoalveolar lavage. Blood eosinophil counts may be normal. Patients usually present with respiratory failure and require intubation. Those treated with corticosteroids respond rapidly; usually within days. Spontaneous recovery has been reported.⁵³ In most cases a causative agent is not

identified, however, recent-onset cigarette smoking has been convincingly linked with AEP.⁵⁴⁻⁵⁸ Repeat exposure to cigarette smoke has consistently resulted in the recurrence of the symptoms, laboratory changes, and physical findings confirming the diagnosis.^{58,59} In a recent report, 18 military personnel deployed in Iraq developed AEP.⁵⁷ All of the patients were cigarette smokers of which 78% were recent onset. All 6 of the patients who underwent bronchoalveolar lavage demonstrated marked eosinophilia.

AEP may be mistaken for other diseases including severe community-acquired pneumonia and acute respiratory distress syndrome (ARDS). Distinguishing AEP from ARDS is crucial given the differing responses to corticosteroids. Those with AEP respond rapidly to steroids whereas those with ARDS do not benefit and have a poor prognosis.

HISTOPATHOLOGIC FINDINGS

AEP shows findings of diffuse alveolar damage coupled with interstitial and alveolar infiltrates of eosinophils. Diffuse alveolar damage is a pattern of acute lung injury

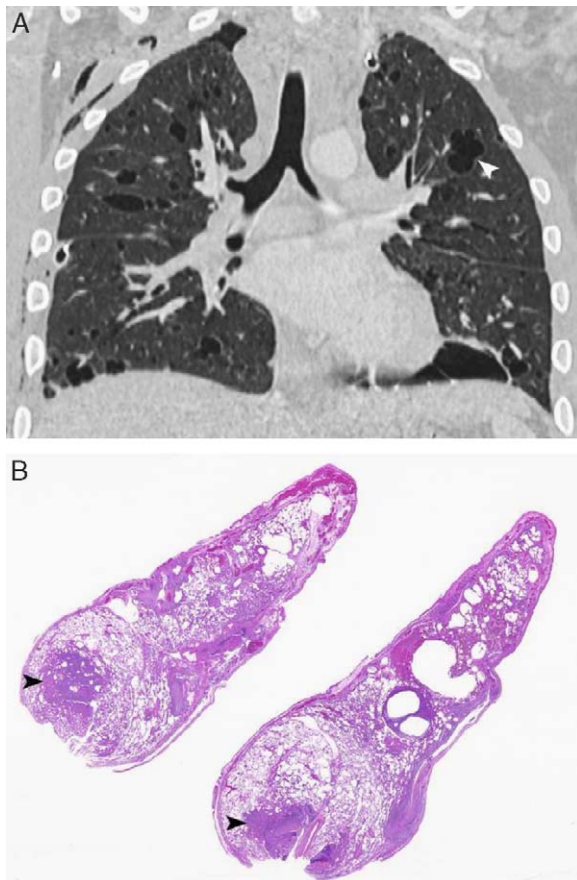


FIGURE 9. Pulmonary Langerhans' cell histiocytosis with cysts alone. A, Coronal reconstruction of computed tomography data demonstrates diffuse involvement of both lungs with thin-walled cysts, some of which are bizarrely shaped (arrowhead). B, In addition to large parenchymal spaces, bronchiocentric nodules (arrowheads) are present histologically (hematoxylin and eosin, 1 ×).

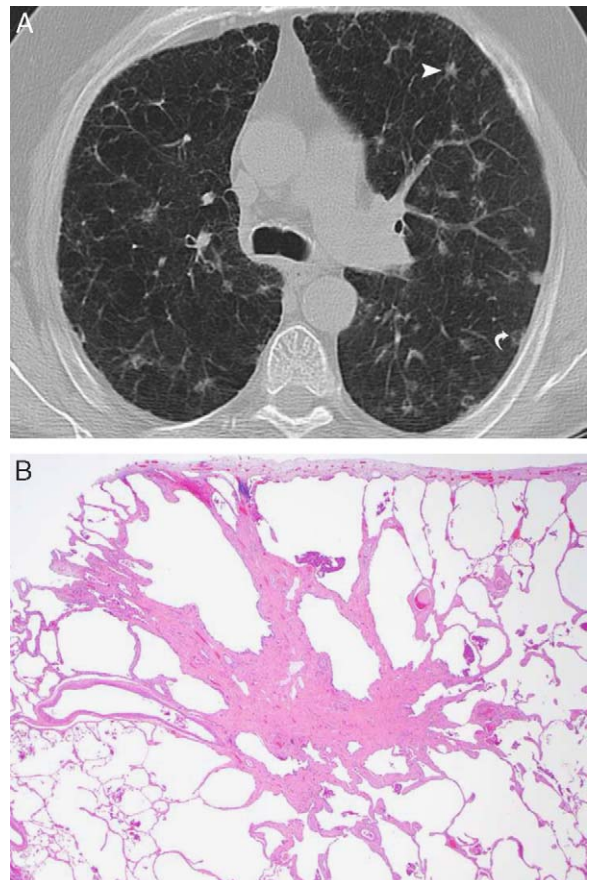


FIGURE 10. Late stage pulmonary Langerhans' cell histiocytosis. A, Axial computed tomography section at the level of the carina demonstrates diffuse low attenuation consistent with emphysema and numerous stellate nodules (arrowhead), some of which are cavitory (curved arrow). B, In contrast to cellular early stage lesions, late stage lesions are composed primarily of fibrous tissue accompanied by adjacent, so-called "pericatricital" airspace enlargement, which tends to accentuate the characteristic stellate morphology of pulmonary Langerhans' cell histiocytosis (hematoxylin and eosin, 20 ×).

characterized in the acute phase by hyaline membranes, interstitial and intra-alveolar edema, patchy type II pneumocyte hyperplasia, and microthrombi (Fig. 11C). The acute phase forms a continuum with the organizing phase in which proliferation of interstitial fibroblasts, organizing alveolar exudates, and prominent type II pneumocyte hyperplasia are the histologic hallmarks.

RADIOLOGIC FINDINGS

On chest radiography those with AEP demonstrate bilateral reticular opacities, commonly with Kerley B (septal) lines. There is rapid progression over hours to days with increasing bilateral areas of patchy or diffuse consolidation. Computed tomography scans demonstrate bilateral areas of ground-glass, consolidation and septal thickening (Fig. 11).⁵⁴ Unilateral or bilateral pleural effusions are present at some point during the course of the illness in all patients. The radiologic findings are similar to those of

pulmonary edema although the heart size is usually normal. The radiologic differential includes ARDS, although septal lines are less common, pulmonary hemorrhage and infection.

INTERRELATIONSHIP OF SMOKING-RELATED LUNG DISEASES

Pigmented macrophages are found in and around the airways of all cigarette smokers. Those same macrophages may have a more extensive distribution and those patients currently carry the label of DIP. Dyspneic smokers who come to clinical attention demonstrate varying combinations of emphysema, airway inflammation/fibrosis, and alveolar wall fibrosis in addition to changes of PLCH. AEP is a dramatic response to recent-onset smoking seen in a small number of individuals. The interconnected pathways that lead to lung inflammation and fibrosis in cigarette smokers are slowly coming into focus (Fig. 1).^{2,3}

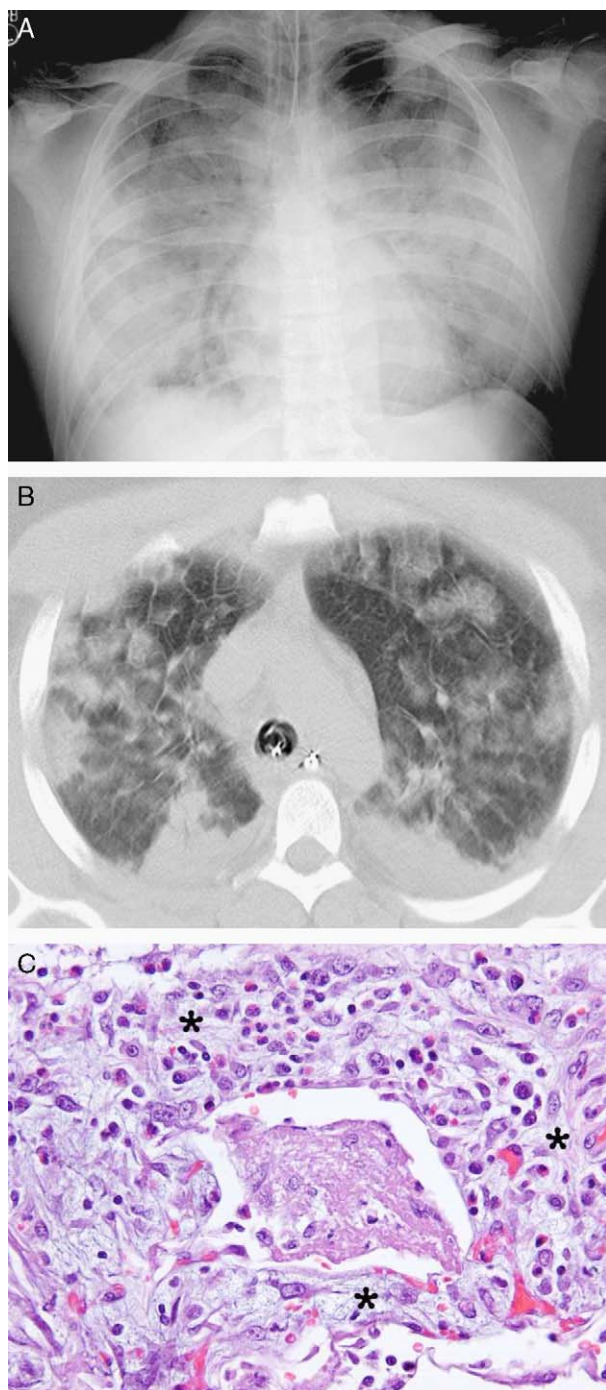


FIGURE 11. Acute eosinophilic pneumonia and respiratory failure in a patient who recently started smoking. A, Anteroposterior portable chest radiograph demonstrates widespread consolidation in an intubated patient. B, Axial chest computed tomography scan demonstrates septal lines, patchy areas of consolidation and small bilateral effusions. C, Widened alveolar walls (asterisks) due to edema and cellular infiltrates largely composed of eosinophils (hematoxylin and eosin, 400 ×).

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