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Review Article

Smoking-Related Interstitial Lung Disease: CT Image-Based Review and Update

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Abstract: Tobacco smoking is the leading cause of preventable deaths in the United States. Beyond the risks of cardiovascular disease and several cancers, smoking contributes to lung inflammation, lung destruction, and smoking-related interstitial lung diseases (SRILD). SRILD describes a broad range of conditions that includes respiratory bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, pulmonary Langerhans cell histiocytosis, acute eosinophilic pneumonia, idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema, interstitial lung abnormality, and smoking-related interstitial fibrosis.

Computed tomography (CT) is central to the diagnosis and understanding of clinicopathologic manifestations of smoking-related lung injury. Common features of SRILD on CT include low-attenuation areas, ground-glass opacities, fibrosis, and lung nodules. Although the various SRILDs are often described as distinct entities, they may manifest with nonspecific features or exhibit mixed patterns and may more accurately be described as a continuum of pathology. Understanding the broad range of radiologic features and recognizing the potential coexistence and overlap of disease processes is essential to maintaining an appropriate differential diagnosis. In this article, we review the radiologic findings associated with SRILDs with a focus on diagnostic considerations and challenges when interpreting CT images.

Keywords: *smoking-related interstitial lung disease, interstitial lung disease, emphysema, computed tomography*

Key Points

- The clinical, pathologic, and radiologic features of smoking-related interstitial lung diseases overlap and often coexist, suggesting that they may be part of a continuum of pathologic processes.
- The distribution, pattern, and types of emphysema, ground-glass opacities, bronchiectasis, reticulations, interstitial thickening, and focal opacities are essential details to the accurate characterization of smoking-related interstitial lung disease.
- Understanding the broad range of radiologic features and recognizing the potential coexistence and overlap of disease processes is essential to maintaining an appropriately broad differential diagnosis.

Introduction

Tobacco smoking is the leading cause of preventable deaths in the United States.[1] In addition to conferring an increased risk of death from cardiovascular disease and several cancers, tobacco smoking contributes to the development of three categories of lung response, which may occur separately or in combination: lung inflammation, lung destruction, and smoking-related interstitial lung disease (SRILD).[1,2] The term *SRILD* refers to a group of lung diseases caused by exposure to cigarette smoke. SRILD can be subdivided into different diseases by clinical presentation, imaging features, and histopathology (Table). These diseases include

Abbreviations
AEP: acute eosinophilic pneumonia
ARDS: acute respiratory distress syndrome
BAL: bronchiolar alveolar lavage
CPFE: combined fibrosis and emphysema
CT: computed tomography
DIP: desquamative interstitial pneumonia
DLCO: diffusing capacity of the lungs for carbon monoxide
HRCT: high-resolution computed tomography
ILA: interstitial lung abnormality
IPF: idiopathic pulmonary fibrosis
NSIP: nonspecific interstitial pneumonia
PFTs: pulmonary function tests
PLCH: pulmonary Langerhans cell histiocytosis
RB: respiratory bronchiolitis
RBILD: respiratory bronchiolitis–interstitial lung disease
SRIF: smoking-related interstitial fibrosis
SRILD: smoking-related interstitial lung disease

respiratory bronchiolitis (RB), respiratory bronchiolitis-associated interstitial lung disease (RBILD), desquamative interstitial pneumonia (DIP), pulmonary Langerhans cell histiocytosis (PLCH), acute eosinophilic pneumonia (AEP), idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE), smoking-related interstitial fibrosis (SRIF), nonspecific interstitial fibrosis (NSIP), and interstitial lung abnormality (ILA). These conditions are characterized by specific imaging, clinical, and pathologic features and, as such, have traditionally been viewed as distinct entities. However, features of these conditions commonly overlap and coexist on a spectrum that includes more common tobacco smoking-related lung injuries such as emphysema.[2,3]

SRILD can be evaluated by chest radiography, computed tomography (CT), and magnetic resonance imaging (MRI); however, the superior spatial resolution and widespread availability of CT renders it the clinical mainstay of SRILD evaluation for diagnosis, grading of severity, and disease surveillance.[3,4] We review the CT features associated with SRILD, explore diagnostic pitfalls, and discuss the clinical implications of each feature. CT imaging findings common to all types of SRILD will be discussed first, followed by a comprehensive review of the recognized entities that exist on the SRILD spectrum of disease.

Common CT Features Among Smoking-Related Interstitial Lung Diseases

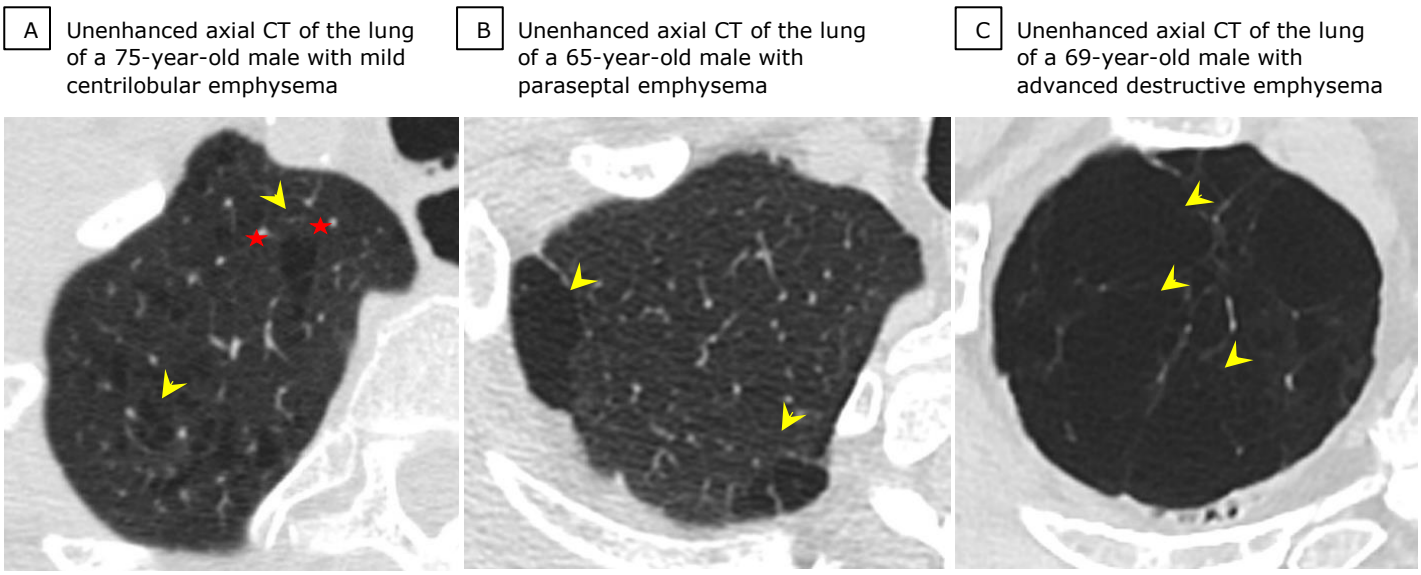
Common CT imaging features of SRILD subtypes include regions of low attenuation, ground-glass opacities, reticulation, architectural distortion from fibrosis, and nodules.

Signs of SRILD include a constellation of CT findings that includes interstitial thickening, linear or irregular reticulations, ground-glass opacities, traction bronchiectasis and bronchiolectasis, and overt honeycombing.[5] These features may exist in isolation or combination. Ground-glass opacities typically correspond to areas of inflammation or submacroscopic interstitial fibrosis, usually distinguishable by a waxing and waning character with the former or persistence over time with the latter.[5] Linear or irregular reticulations should be further characterized by their distribution—bronchocentric or subpleural.[5] Linear bands are often associated with airway-associated inflammation or post-inflammatory scarring.[4,5] Subpleural predominant reticulations may be observed in patients with either ILA or overt fibrosis.[5,6] Diagnostic certainty for irreversible fibrosis increases when there is clear evidence of architectural distortion, such as irregular reticulations, traction bronchiolectasis, or overt honeycombing in affected regions.[6]

Low-Attenuation Regions

Low lung attenuation is one of the most common features of SRILD on CT due to emphysema or air trapping related to smoking-related airways disease. Emphysema is defined pathologically as airspace dilatation and destruction beyond the terminal bronchioles, which is the result of smoking-related airway inflammation. Smoking-related emphysema can be categorized as centrilobular (Figure 1A) or paraseptal (Figure 1B) depending on the pattern and anatomic location of destruction.[7] Centrilobular emphysema is highly associated with smoking and involves the

Figure 1. Different Emphysema Morphologies on CT Imaging.



Mild centrilobular emphysema (A) is characterized by dilated airspaces in the center of the pulmonary lobule, which are seen on CT as areas of low attenuation (A, yellow arrowheads) surrounded by normal lung parenchyma (A, red stars). Paraseptal emphysema (B) involves dilated airspaces (B, yellow arrowheads) along the lung periphery, seen on CT with low attenuation. Advanced destructive emphysema (C) is defined by dilated airspaces that destroy the lung parenchyma. On CT, dilated low-attenuation spaces (C, yellow arrowheads) are visualized with no normal intervening lung parenchyma.

destruction of respiratory bronchioles within an acinus, initially sparing the alveoli near the lobular septum. As centrilobular emphysema progresses, multiple primary lesions coalesce, ultimately involving an entire secondary pulmonary lobule in a process that is distinguished from true panlobular emphysema by the absence of α-1 antitrypsin deficiency.[7] The Fleischner Society[7] recently applied the terms *confluent* emphysema and *advanced destructive* emphysema (Figure 1C) to describe progressive stages of severe centrilobular emphysema.

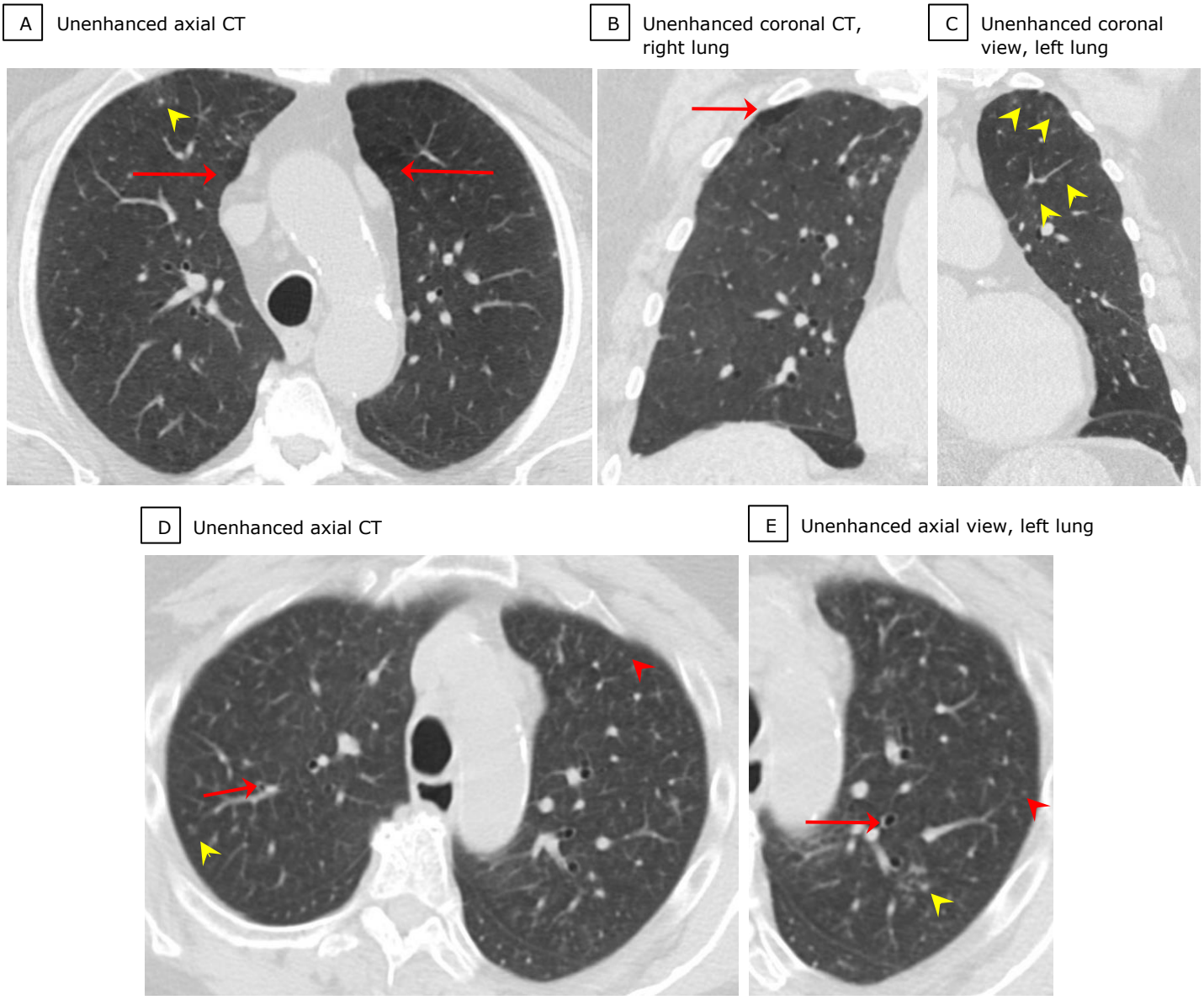
Regardless of its pattern, emphysema is visualized on CT with hyperlucent areas of low attenuation that, in advanced stages, may be associated with lung overexpansion due to insufficient emptying of the emphysematous regions on exhalation.

Patchy patterns of low attenuation may also be observed in patients with smoking-associated large and small airways disease.[4,8] On inspiratory scans, alternating regions of normal and low lung attenuation are referred to as *mosaic oligemia*, in which the oligemic regions are featureless and of relatively low lung attenuation due to air trapping and constriction of the regional vasculature.[4,7] In these patients, regional air trapping is due to premature small airways closure or airway mucostasis.[4,8] This can be confirmed with expiratory imaging at suspended residual volume, which exaggerates the differences in attenuation between normal and oligemic lung parenchyma.[8] In some instances, air trapping may be difficult to distinguish from advanced destructive emphysema.[9]

Lung Nodules

Discrete lung nodules of solid or subsolid consistency are often observed in the lungs of smokers on CT and can reflect areas of inflammation, fibrosis, or neoplastic disease.[10] Smoking-related lung nodules have a predilection for the upper lobes, particularly the right upper lobe.[10] This anatomic predilection has been ascribed to differences in lung perfusion and ventilation.[10] Gravity results in the lung apices having a greater ventilation-to-perfusion ratio, while the lower lobes are relatively over-perfused. Lymphatic drainage, driven by perfusion, is slower in the apices. As a result, the lung apices are exposed to greater levels of toxic inhalants and suffer from slower removal of small particulates relative to the lower lobes.[11] Due to the

Figure 2. Respiratory Bronchiolitis and Respiratory Bronchiolitis-Associated Interstitial Lung Disease.



(A-C) Unenhanced axial and coronal CT images in a 76-year-old man with biopsy-proven respiratory bronchiolitis-associated interstitial lung disease (RBILD). Bilateral paraseptal emphysema (A and B, red arrows) in the upper lobes with foci of centrilobular micronodular ground-glass opacities (A and C, yellow arrowheads).
(D, E) Unenhanced axial CT images in an asymptomatic 65-year-old woman with RB. Bronchial and bronchiolar wall thickening (D and E, red arrows) with diffuse centrilobular micronodules (D and E, red arrowheads) and ground-glass opacities with centrilobular prominence (D and E, yellow arrowheads).

bronchiolar distribution of smoke during inhalation, nodules and additional signs of injury commonly occur in a centrilobular distribution.[9] While multiple patterns of lung injury can coexist in the same patient, certain radiological features assist in establishing a predominant disease pattern. A multidisciplinary approach is desirable to achieve an accurate diagnosis.[12]

Types of Smoking-Related Interstitial Lung Diseases

Respiratory Bronchiolitis and Respiratory Bronchiolitis-Associated Interstitial Lung Disease

Respiratory Bronchiolitis (RB) is a histologic finding indicative of an inflammatory response of lung tissue and small airways to cigarette smoke and is found in nearly all smokers.[9] It is characterized histologically by brown pigmented macrophages within respiratory bronchioles and adjacent alveoli.[13] RB is usually clinically silent. The more advanced form of the condition is referred to as *respiratory bronchiolitis-associated interstitial lung disease* (RBILD) and is distinguished by the presence of respiratory symptoms, most commonly cough and exertional dyspnea.[14] Abnormalities in pulmonary function tests (PFTs) are a defining feature of RBILD and show either a mixed or predominantly restrictive pattern with a mild to moderate reduction in the diffusing capacity of the lungs for carbon monoxide (DLCO).[12,13,15] Although interstitial lung diseases usually manifest with low lung volumes, the frequent co-occurrence of emphysema with RBILD can lead to paradoxically normal lung volumes. In such cases, the reduction in DLCO may be greater than that expected with isolated emphysema.[15,16]

The most common CT imaging features of RB and RBILD include patchy ground-glass opacities in a bronchiolocentric distribution, bronchial wall thickening, and characteristic centrilobular ground-glass nodules (Figure 2), with these features appearing with greater severity in RBILD than in RB.[9,17] These findings have an upper lobe predominance, and patients may have associated centrilobular emphysema. Fibrosis is uncommon, typically mild, and limited to the peribronchiolar interstitium when present.[16] When RBILD is suspected, the primary differential considerations include subacute hypersensitivity pneumonitis, DIP, and NSIP. The documentation of an almost invariable smoking history, presence of upper lobe emphysema, and brown pigmented macrophages demonstrated in bronchoalveolar lavage (BAL) fluid may help distinguish between these conditions, as hypersensitivity pneumonitis is rare in smokers.[2,9,14] Similarly, a history of exposure to environmental antigens makes hypersensitivity pneumonitis more likely, as does lymphocytosis in bronchoalveolar lavage fluid. The CT findings in patients with RB and RBILD vary after smoking cessation.[4,18] In some patients, bronchial wall thickening, ground-glass attenuation, and centrilobular micronodules regress. In others, CT appearances persist and may relate to the persistence of peribronchiolar fibrosis or emphysema.[15,19]

Desquamative Interstitial Pneumonia

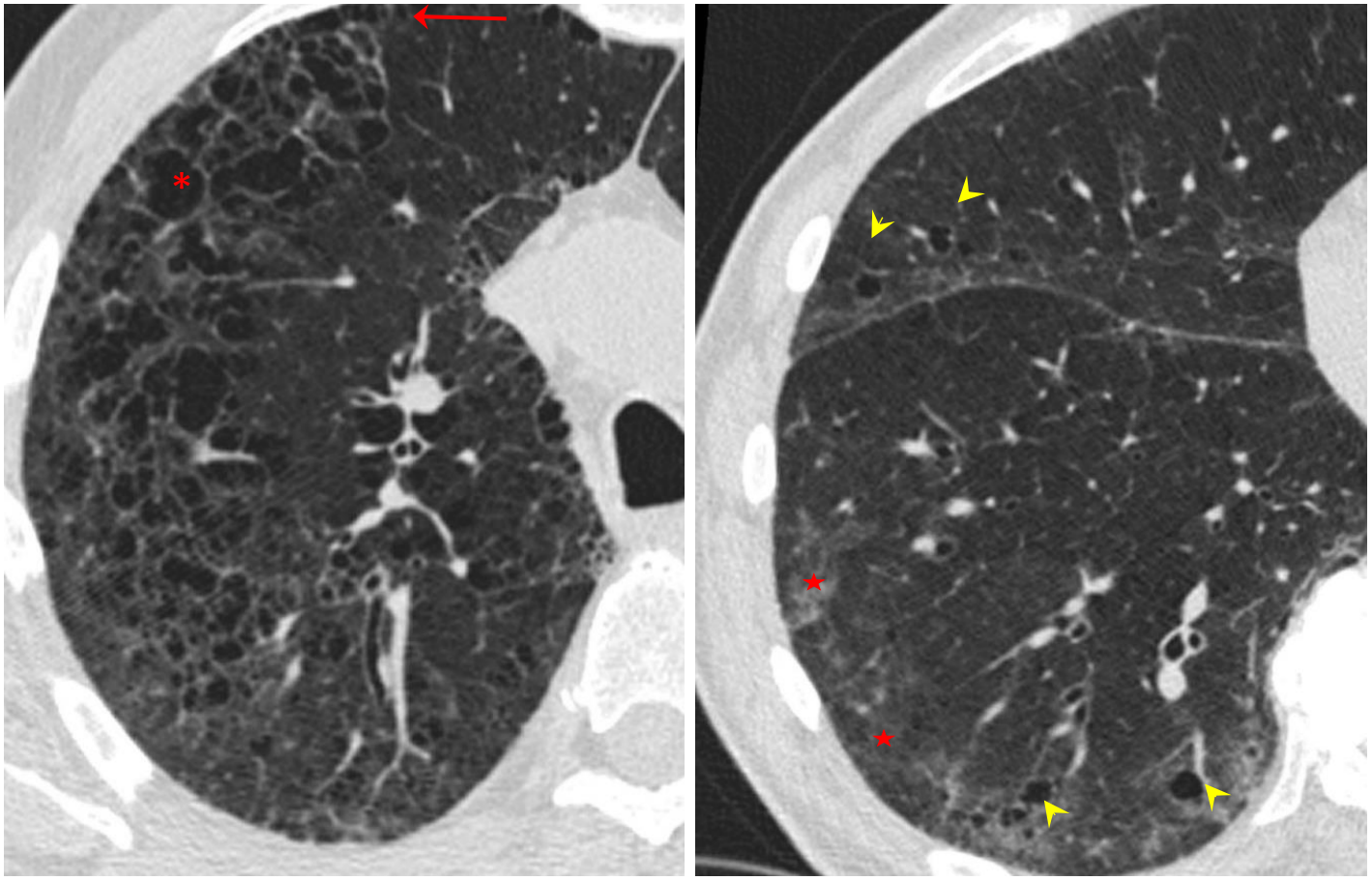
The term *desquamative interstitial pneumonia* (DIP) is a misnomer, as the entity that was originally thought to be due to alveolar filling by epithelial cell desquamation is now known to be the result of alveolar macrophage accumulation.[20] This condition is much less common than RB/RBILD, and patients typically have more severe symptoms such as insidious dyspnea, cough, hypoxemia, and reduced DLCO. A high percentage of patients with DIP develop nail clubbing in their fourth to sixth decades.[13]

The predominant CT appearance of DIP is that of bilateral, patchy peripheral or diffuse ground-glass opacification with a subpleural and basal distribution (Figure 3).[18] The basilar, lower lobe distribution of ground-glass opacities distinguishes DIP from RB/RBILD, which predominates in the upper lobe. Small cystic lucencies with irregular shapes may also develop within the regions of ground-glass opacification (Figure 3B).[21] Progression to honeycombing is uncommon. When diffuse, the ground-glass opacities in DIP are difficult to distinguish from those seen in the other SRILDs, rendering the combination of irregularly shaped, thin-walled, cystic lucencies and ground-glass opacities the best-defining imaging features of DIP.[22] A subpleural distribution of ground-glass opacities can aid in differentiating DIP from NSIP, the latter of which classically, though not uniformly, spares the subpleural lung.[21] Significant clinical symptomatology, observed in DIP, is also useful for diagnosis.

Figure 3. Unenhanced Axial CT Scan in an 80-Year-Old Man with Desquamative Interstitial Pneumonia (DIP).

A Axial CT through the right upper lobe

B Axial CT through the right middle and lower lobes



(A) Confluent centrilobular (A, red asterisk) and substantial paraseptal emphysema (A, red arrow) are present in the right upper lobe. (B) DIP is seen as lower-lung-predominant areas of peripheral ground-glass opacification (B, red stars) with characteristic intermixed cystic spaces (B, yellow arrowheads).

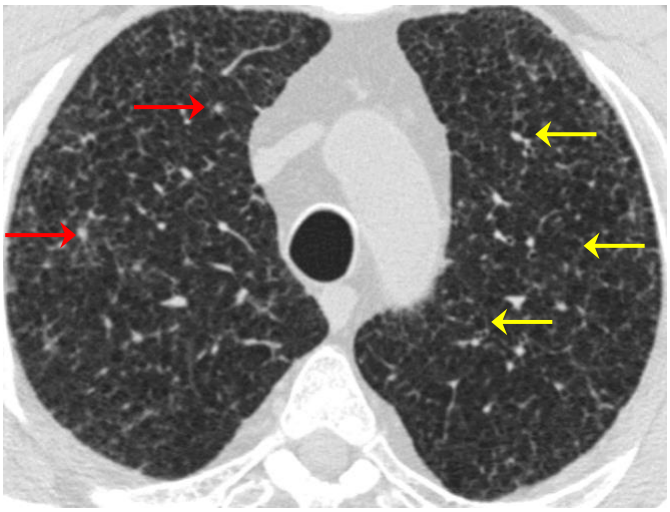
Pulmonary Langerhans Cell Histiocytosis

Pulmonary Langerhans Cell Histiocytosis (PLCH) is a rare SRILD caused by an infiltration of the pulmonary alveoli by histiocyte cells.[23] This results in the formation of peribronchiolar stellate-shaped nodules, most often comprised of Langerhans cells. The collection of histiocytes destroys the bronchiolar wall with resultant central cavitation and eventual small airway dilation.[23] Cigarette smoking is a major risk factor for developing PLCH, which occurs more commonly in individuals of Asian or African descent.[24] Although most patients are asymptomatic, symptoms may include cough, shortness of breath, fatigue, and weight loss.[24,25] Approximately 15-20% of patients present with pneumothorax as the initial clinical finding[26] due to rupture of the cysts and small cavities into the pleural space.

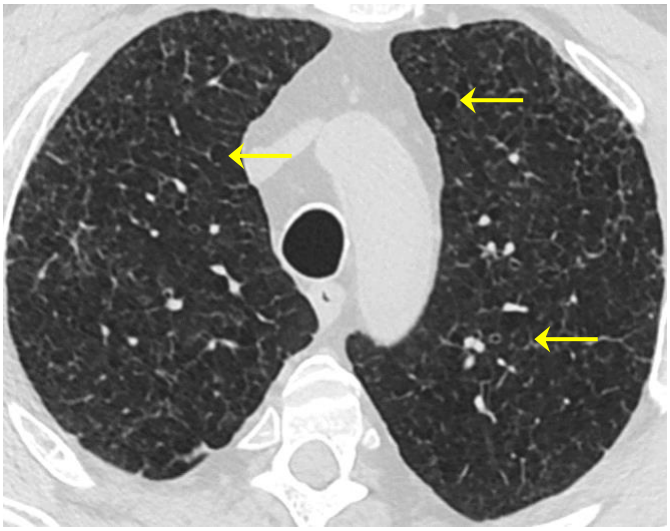
The defining radiologic features of PLCH depend on the timing of the high-resolution computed tomography (HRCT) obtained during the patient's disease course. Early in the disease process, the nodular collection of Langerhans cells is reflected on HRCT as centrilobular nodules of soft tissue attenuation and cysts, predominantly in the mid-to-upper lungs, sparing the lung bases (Figure 4A).[27] As the disease advances and small airways are destroyed, large nodules become cystic, initially with thick walls, and ultimately progress to thin-walled cysts with irregular shapes (Figure 4B).[27] Eventual fibrotic changes follow the same distribution.

Figure 4. Axial CT of the Lungs of a 70-Year-Old Man with Biopsy-Proven Respiratory Bronchiolitis (RB) and Pulmonary Langerhans Cell Histiocytosis (PLCH).

A Initial unenhanced CT



B Unenhanced CT obtained 25 months after diagnosis



(A) Bronchial wall thickening and numerous centrilobular nodules (A, red arrows) are visible in addition to small thin-walled cysts (A, yellow arrows).
(B) Twenty-five months after smoking cessation, nodularity decreased, but thin-walled cysts persisted (B, yellow arrows).

PLCH should be differentiated from advanced emphysema and lymphangioleiomyomatosis, the latter of which has more rounded, thin, regular, smooth walled, and uniformly distributed cysts.[25] The mid-to-upper-lung distributions of nodules in PLCH are helpful in distinguishing it from differential considerations such as sarcoidosis, pulmonary metastasis, and infections.

Acute Eosinophilic Pneumonia

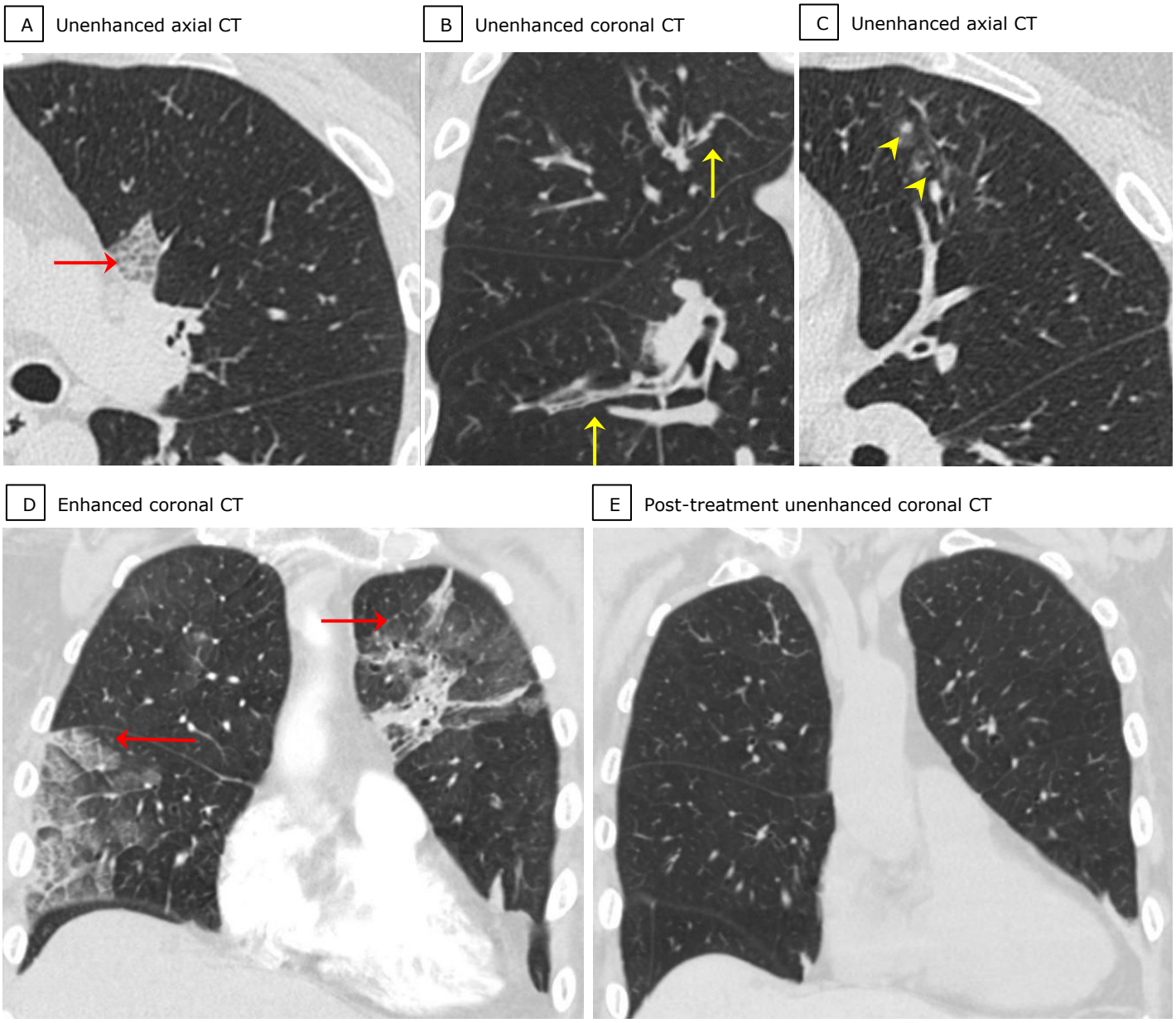
Acute eosinophilic pneumonia (AEP) is an uncommon disease characterized by acute febrile illness, often triggered by the inhalation of antigens such as tobacco and, less commonly, various drugs such as antibiotics, illicit drugs, anti-inflammatory drugs, and even electronic cigarettes.[28-30] Changes in smoking patterns, including recent onset or increases in smoking frequency, may contribute to the development of AEP in smokers.[31] The clinical presentation can resemble acute respiratory distress syndrome (ARDS) with patients experiencing hypoxemia, cough, dyspnea, and acute respiratory failure.[32] There is often a histologic pattern of diffuse alveolar damage with eosinophilic interstitial and alveolar infiltrates.[33] In the absence of treatment, rapid progression of clinical and imaging findings is common.

A combination of extensive patchy bilateral ground-glass opacities and smooth interlobular septal thickening are common features on CT (Figure 5).[34,35] Thickening of the bronchovascular bundles, pleural effusions, and ill-defined centrilobular nodules are also commonly observed. Fibrosis and emphysema, however, are not characteristic of AEP.[33,35] The relatively nonspecific radiographic features of AEP overlap with conditions such as pulmonary edema, diffuse alveolar damage, pulmonary hemorrhage, and atypical infections, making it challenging to diagnose. High suspicion based on a patient's smoking habits in the context of an acute febrile illness is important to establish the diagnosis. Fortunately, most patients respond well to corticosteroids, with response to therapy confirming the diagnosis.[36]

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is the most common chronic and progressive form of idiopathic interstitial pneumonia of unknown etiology and is associated with a UIP pattern on histopathology. Cigarette smoking has been identified as a risk factor in developing IPF.[37-39]

Figure 5. Computed Tomography (CT) images of Acute Eosinophilic Pneumonia (AEP).

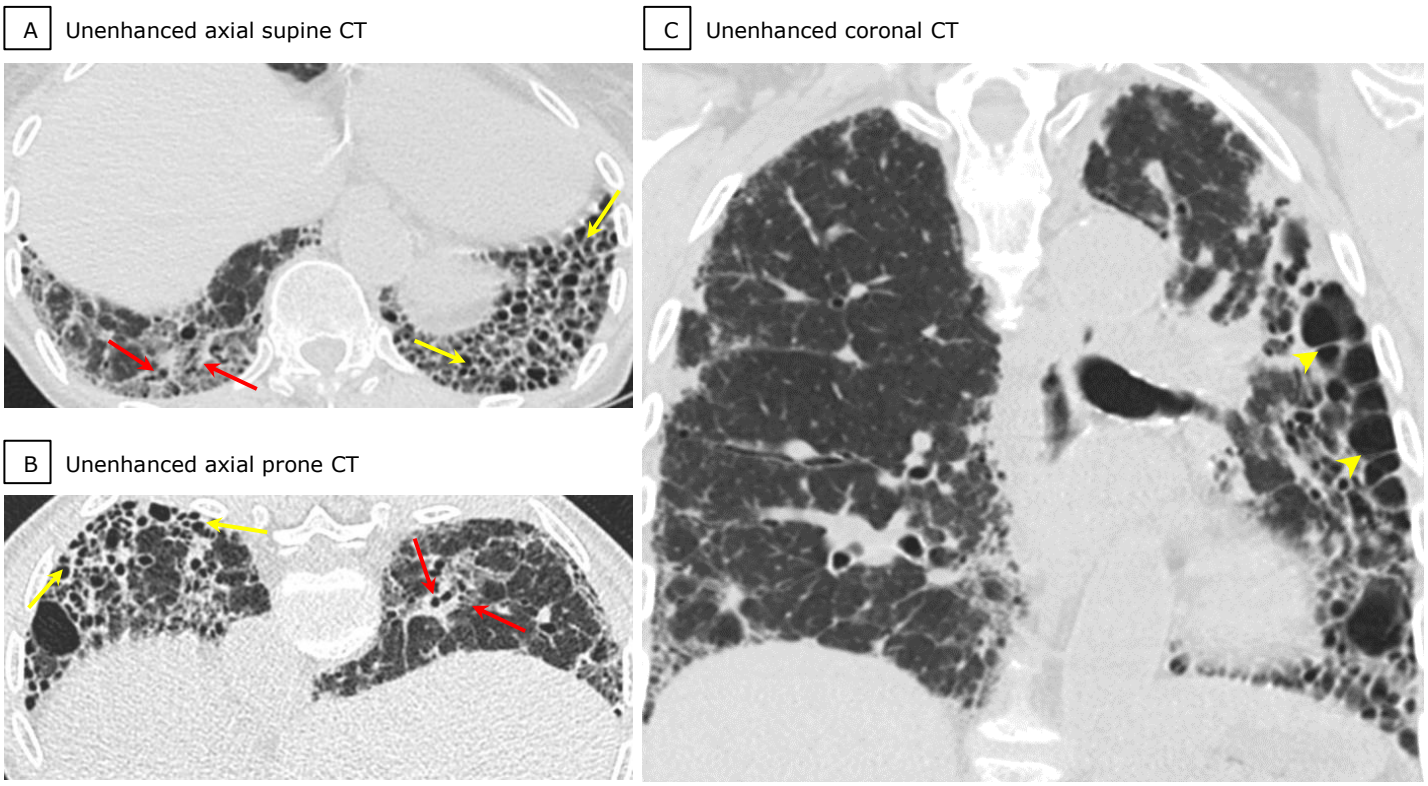


(A-C) Unenhanced CT images in a 45-year-old man with a biopsy-proven recurrence of AEP. (A) Axial image depicting focal ground-glass opacification with inter- and intralobular septal thickening (A, red arrows). (B) Coronal image of diffuse airway wall thickening (B, yellow arrows). (C) Axial image of ill-defined centrilobular nodules (C, yellow arrowheads).
(D, E) CT of the lungs of an 87-year-old woman with biopsy-proven AEP with improvement after prednisone. (D) Enhanced coronal CT image shows ground-glass consolidations with inter- and intralobular septal thickening that persist after course of antibiotics (D, red arrows). (E) Following corticosteroid therapy, symptoms and consolidations resolved completely.

Patients often experience refractory dry cough, worsening dyspnea on exertion, digital clubbing, and a restrictive pattern on PFTs with decreased DLCO.[40]

HRCT findings of IPF consist of irregular reticular opacities in a subpleural and basilar predominant distribution, traction bronchiectasis and bronchiolectasis, ground-glass opacification in fibrotic areas, overt honeycombing (especially if more than 8% of lung parenchyma is involved), and other evidence of lung architectural distortion reflecting fibrosis (Figure 6).[41,42]

Figure 6. Unenhanced CT of the Lungs of a 75-Year-Old Woman with a History of IPF.



(A) Axial supine and (B) axial prone images demonstrate basilar predominant coarse irregular reticulations, bronchiolectasis (A and B, red arrows), and overt honeycombing (A and B, yellow arrows). (C) Coronal image of paraseptal bullous disease (C, yellow arrowheads) with architectural distortion.

The spatiotemporal heterogeneity of fibrotic lesions of varying severities on histologic sampling is an informative finding that supports the diagnosis of IPF.[43] Alternative diagnostic considerations should be prompted if the following features are present: mid-to-upper-lobe predominance of fibrosis, extensive ground-glass opacities, nodules or cysts, pleural effusion, or predominant consolidation.[44]

Combined Pulmonary Fibrosis and Emphysema

Combined pulmonary fibrosis and emphysema (CPFE) is a syndrome (i.e., cluster of clinical and radiologic manifestations with clinically relevant implications or major pathogenetic significance)[45] that remains to be elucidated.[46] CPFE is considered a distinct condition reflecting the coexistence of emphysema and fibrotic lung disease. Patients often have preserved lung volumes, thought to be due to the opposing effects of emphysema and fibrosis, and reduced DLCO.[47] Clinical symptoms are similar to emphysema and IPF with cough and dyspnea.[47] Patients with CPFE are at an increased risk of developing lung cancer,[47] and a retrospective analysis[48] found that 47-90% of CPFE patients are diagnosed with pulmonary hypertension. Patients with CPFE also have higher all-cause mortality than those with fibrosis or emphysema alone and a poorer prognosis than those with IPF alone.[49] Clinically, CPFE is not uncommon, with a 25-50% prevalence of emphysema in patients with IPF.[49]

On diagnostic imaging, the appearance of CPFE is heterogeneous, with variations in the types of fibrosis and emphysema that are seen concurrently, though the majority of studies investigating CPFE have focused on individuals with known IPF or UIP pattern fibrosis.[50] Pulmonary fibrosis involving the lower lobes in the form of irregular reticular opacities with honeycombing, traction bronchiectasis, or architectural distortion are common findings.[50] Emphysema in CPFE, whether centrilobular or

paraseptal emphysema, often presents in an upper lobe distribution.[50] Paraseptal emphysema is more prevalent in CPFE than in COPD.[47] Superimposition of emphysema and fibrosis can result in the formation of what have been termed thick-walled cysts[51] or traction emphysema[50] in the posterobasal lung, a finding more commonly seen in CPFE than in isolated IPF.[51]

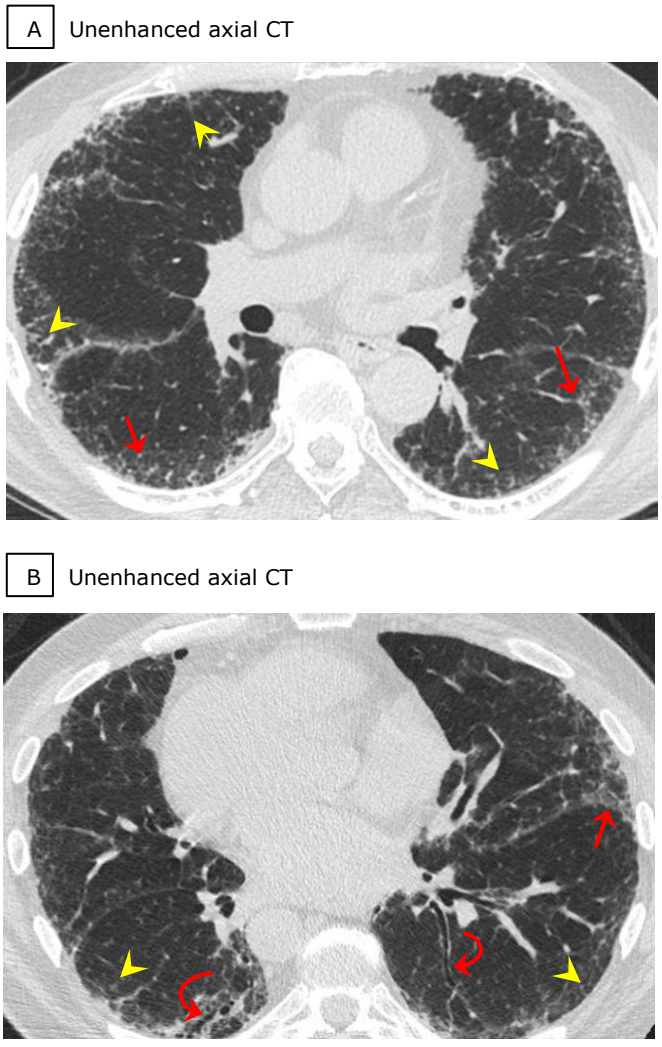
The histopathologic identification of CPFE is also challenged by heterogeneity. For example, emphysema, a required component for the diagnosis of CPFE, can occur alongside several smoking-related abnormalities, including smoking-related interstitial fibrosis (SRIF).[50] A distinct pattern of fibrosis linked to cigarette smoking, SRIF demonstrates minimal inflammation and expansion of the alveolar septa by eosinophilic collagen deposits on histology[52] and is frequently seen on histologic analysis of lung tissue from smokers, with rates as high as 45% in an analysis of lobectomy specimens.[53] In isolation, SRIF is often clinically occult,[52] and imaging findings are not well established—though one case series identified bilateral ground-glass opacities as a dominant feature.[54] Histologic findings of SRIF overlap with those of RBILD with fibrosis, RB with fibrosis, airspace enlargement with fibrosis (AEF),[54] and DIP.[55] While SRIF has been theorized to account for the thick-walled cysts characteristic of CPFE,[56] isolated SRIF is not known to be a driver of CPFE, and current guidance for the histopathologic diagnosis of CPFE suggests that emphysema must be accompanied by an additional form of fibrosis.[46] Similarly the fibrotic form of PLCH, though it may coexist with emphysema, is an additional entity that in isolation is not sufficient to fill the fibrotic requirement of CPFE.[46,47]

Nonspecific Interstitial Pneumonitis

Nonspecific interstitial pneumonitis (NSIP) is the second most common pattern of all forms of ILD and consists of two subtypes: cellular and fibrotic, the latter being more common and associated with worse outcomes.[57] Smoking has only recently been considered as a direct cause of NSIP.[58,59]

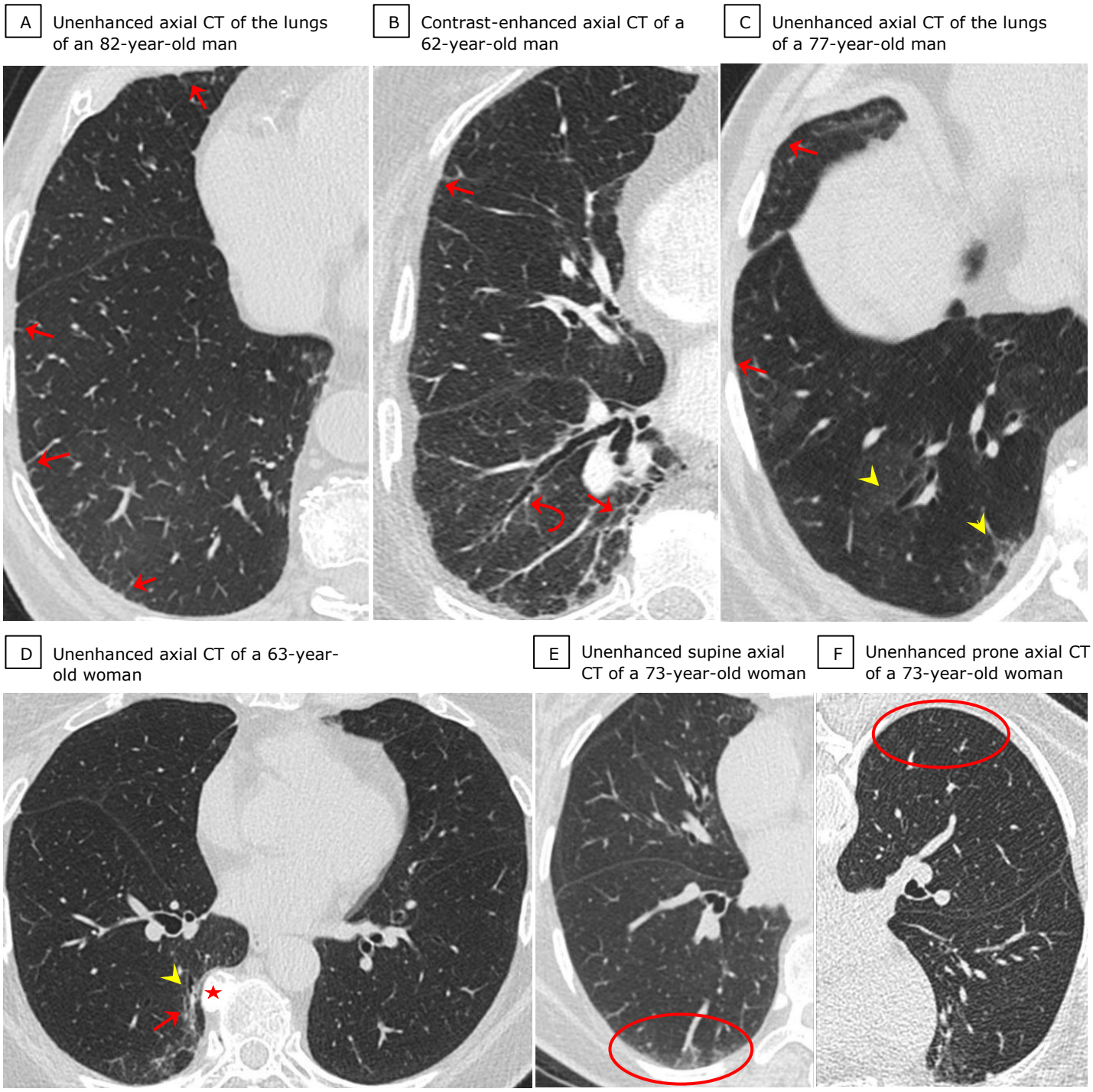
On CT, both fibrotic and cellular NSIP present with symmetric bilateral ground-glass opacification, predominantly in the lower lungs (Figure 7). Subpleural sparing is inconsistently seen, but when present is relatively specific for diagnosis. Fibrotic NSIP is distinguished from cellular NSIP by the presence of fine reticulations and traction bronchiectasis/bronchiolectasis in addition to ground-glass opacities (Figure 7). Less commonly, honeycombing and consolidation can be seen in fibrotic NSIP. In smokers and those with fibrotic NSIP, traction bronchiectasis/bronchiolectasis and a reticular opacity to ground-glass opacity ratio are useful in distinguishing NSIP from UIP (a ratio

Figure 7. Unenhanced Axial CT Images of a 71-Year-Old Female with Biopsy-Proven Nonspecific Interstitial Pneumonia (NSIP).



(A, B) Moderate fibrotic NSIP with bilateral peripheral ground-glass opacification (A, B, red arrows), peripheral reticulation (A, B, yellow arrowheads) and (B) bronchiolectasis (B, curved red arrows).

Figure 8. Various Appearances of Interstitial Lung Abnormalities (ILA) and ILA Mimics.



(A) Axial unenhanced CT image shows peripheral reticulations (A, red arrows) with characteristic involvement of the anti-dependent and dependent surfaces. (B) Axial contrast-enhanced CT image demonstrating fibrotic ILA with anti-dependent and dependent peripheral reticulations (B, red arrows) as well as bronchiectasis (B, red curved arrow). (C) Axial image shows ground-glass predominant ILA with dependent and anti- dependent peripheral reticulations (C, red arrow) as well as discreet ground-glass opacity (C, yellow arrowheads). (D) Axial unenhanced CT demonstrates focal right lower lobe paraspinous reticulation and ground-glass opacity (D, red arrow) and focal traction bronchiectasis (D, yellow arrowhead) subjacent to a prominent spinous osteophyte (D, red star), without involvement of other portions of lung or anti-dependent lung subjacent. Findings are characteristic of focal mechanical fibrosis and not ILA. (E) Axial supine and (F) prone CT images demonstrate dependent atelectasis mimicking ILA. (E) Ground-glass opacity and reticulation (E, red oval area) is seen only in the dependent lung without involvement of the anti-dependent lung; (F) on prone imaging, these abnormalities resolve (F, red oval area).

≥1 is more common in UIP, with 93% sensitivity and 54% specificity) in smokers without emphysema.[57]

Interstitial Lung Abnormality

Interstitial lung abnormality (ILA) is an evolving descriptor that refers to often-subtle pulmonary parenchymal abnormalities identified on CT in more than 5% of patients without clinical symptoms or suspicion of interstitial lung disease. Studies have demonstrated that 6-20% of smokers have ILA and that the presence of ILA is associated with increased all-cause mortality,[60,61] which reflects the prognostic importance of its identification. A dose-dependent association between the level of cigarette smoke exposure and interstitial abnormalities[62] has also been shown. ILA can be broadly classified by its location and the presence of fibrosis. The classifications are non-subpleural, subpleural nonfibrotic, or subpleural fibrotic.[63] Fibrotic ILA is associated with disease progression on CT.[61]

ILAs are frequently discovered incidentally on CT (Figure 8). Nonfibrotic ILA is most commonly seen as fine reticulations in the lung with a nondependent distribution. Features of fibrotic ILA include ground-glass opacities, cysts, honeycombing and traction bronchiectasis. It is important to note that patients with clinically symptomatic ILD should not be classified as having ILA.[63] The use of consistent terminology will be essential for standardized reporting in future studies investigating the role of ILA in clinical practice.[64]

Conclusion

CT is an invaluable imaging modality that enables comprehensive evaluation of the entire lung, expanding our understanding of SRILD and the etiological role of tobacco smoke inhalation. Although often presented as distinct entities, smoking-related interstitial lung diseases may have nonspecific or mixed features. Understanding the broad range of radiologic features and recognizing the potential coexistence and overlap of disease processes is essential to maintaining an appropriately broad differential diagnosis. Accurately identifying these sometimes-subtle changes on imaging obtained for other indications (such as for lung cancer screening) will ensure early detection of these disease processes when options for therapy and impetus for smoking cessation may be greater. Ultimately, a multidisciplinary approach combining comprehensive imaging evaluation, review of patient clinical presentation and smoking history, and histologic-radiologic correlations is central to deriving the most probable diagnosis.

Author Contributions

Conceptualization – J.J.S., C.H., D.R.A., A.E.P.; Acquisition, analysis, and interpretation of data – J.J.S., C.H., D.R.A., A.E.P.; Writing – original draft preparation J.J.S., C.H., D.R.A., A.E.P.; review and editing J.J.S., C.H., A.S., D.R.A., A.E.P. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

None relevant.

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Table. Smoking-Related Interstitial Lung Diseases (SRILD) by Clinical, Histopathology, and High-Resolution CT Features.

SRILD	Clinical presentation	Histopathology	HRCT findings
Respiratory bronchiolitis (RB) & respiratory bronchiolitis-associated interstitial lung disease (RBILD)	▪ Insidious cough and dyspnea over the course of weeks to months ▪ RBILD is distinguished from RB by more severe respiratory symptoms and abnormal PFTs	▪ Bronchiolocentric distribution of pigmented macrophages within alveoli ▪ Variable alveolar septal wall thickening by mild inflammation or diffuse fibrosis	▪ Centrilobular nodules ▪ Patchy ground-glass opacities ▪ Bronchial wall thickening-upper lobe predominant ▪ Centrilobular emphysema ▪ Expiratory air trapping ▪ Findings of fibrosis absent in RB
Desquamative interstitial pneumonia (DIP)	▪ Exists on a spectrum with RB ▪ Often more significant symptoms of dyspnea ▪ Possible hypoxemia ▪ Possible decreased diffusing capacity	▪ Diffuse distribution of pigmented macrophages with alveoli (more so than with RB) ▪ Variable alveolar septal wall thickening by mild inflammation or diffuse fibrosis	▪ Bilateral patchy, peripheral, or diffuse ground-glass opacities ▪ Reticular opacities ▪ Cystic lucencies with irregular shapes ▪ Possible centrilobular emphysema ▪ Honey combing uncommon
Pulmonary Langerhans cell histiocytosis (PLCH)	▪ Exertional dyspnea, nonproductive cough, fatigue, weight loss ▪ Pneumothorax as first sign (15-20% of patients) ▪ May be asymptomatic	▪ Peribronchiolar, stellate-shaped nodules ▪ Adjacent paracicatricial emphysema ▪ RB with intra-alveolar accumulation of macrophages	▪ Centrilobular nodules of soft tissue attenuation predominating in mid-to-upper lungs ▪ Cavitation within nodules ▪ Cysts in mid-to-upper lungs with progression to thin- or thick-walled cysts with bizarre shapes ▪ Sparing of lung bases
Acute eosinophilic pneumonia (AEP)	▪ Acute febrile illness often triggered by acute changes in smoking habits ▪ Hypoxemia, cough, dyspnea, pleuritic chest pain ▪ Resembles ARDS with acute respiratory failure ▪ Responsive to corticosteroids	▪ Interstitial and alveolar eosinophilic infiltration ▪ Mild lymphocytic infiltrates and scattered giant cells may be present ▪ Diffuse alveolar damage	▪ Extensive, bilateral ground-glass opacities ▪ Smooth interlobular septal thickening (crazy paving) ▪ Ill-defined centrilobular nodules ▪ Thickening of bronchovascular bundles ▪ Fibrosis and emphysema NOT characteristic
Idiopathic pulmonary fibrosis (IPF)	▪ Chronic, progressive disease ▪ Refractory dry cough, worsening exertional dyspnea, dry inspiratory crackles ▪ Possible digital clubbing ▪ Restriction and decreased diffusion capacity on pulmonary function tests	▪ UIP pattern ▪ Fibroblastic foci consisting of clusters of fibroblasts and immature connective tissue in the lung interstitium ▪ Honeycombing with a basilar and subpleural distribution ▪ Temporal heterogeneity with fibrotic lesions of varying stages in the same biopsy specimen (fibroblastic foci, mature fibrosis, and honeycombing)	▪ UIP pattern ▪ Honeycombing (particularly if involving more than 8% of lung parenchyma) ▪ Reticular opacities in the immediate subpleural lung ▪ Ratio of reticular opacity to ground-glass opacity ≥ 1 ▪ Lung architecture distortion reflecting fibrosis ▪ Decreased lung volumes, especially in the lower lobes
Combined pulmonary fibrosis and emphysema (CPFE) †	▪ Combination of emphysema and fibrotic lung disease ▪ Symptoms similar to emphysema and IPF (dyspnea, cough) ▪ May have preserved spirometry but reduced diffusing capacity	▪ Spatiotemporal homogeneity of interstitial thickening due to mild inflammation and chronic fibrosis ▪ Lung architecture usually preserved	▪ Findings may be normal or overlap with RB and DIP ▪ Centrilobular or paraseptal emphysema often upper lobe predominant ▪ Pulmonary fibrosis of lower lobes (reticular opacities with honeycombing, architectural distortion, or traction bronchiectasis)

			▪ Thin-walled cysts
Smoking-related interstitial fibrosis (SRIF)	▪ In isolation, SRIF is clinically occult	▪ Alveolar septa are widened by collagen deposition. ▪ Frequently accompanied by emphysema and respiratory bronchiolitis	▪ SRIF does not manifest as traditional architectural distortion/fibrosis on CT ▪ Bilateral ground-glass opacities were a dominant feature in one case series
Nonspecific interstitial pneumonia (NSIP)	▪ Insidious onset of dry cough, dyspnea, and restrictive pattern on spirometry with reduced diffusing capacity ▪ Fibrotic type (fNSIP) most common ▪ Cellular type less common but carries better prognosis ▪ May have associated autoimmune features	▪ Spatiotemporal homogeneity of interstitial thickening due to mild inflammation and chronic fibrosis ▪ Lung architecture usually preserved	▪ Relatively symmetric bibasilar ground-glass opacities ▪ Traction bronchiectasis ▪ Thickening of bronchovascular bundles ▪ Reticular opacities ▪ UIP features seen in up to 30% of patients
Interstitial lung abnormality (ILA)	▪ Asymptomatic ▪ Nondependent parenchymal abnormalities seen in > 5% of lungs on CT ▪ Dose-dependent association with smoking status and cigarette smoke exposure ▪ Associated with increased all-cause mortality	▪ Not typically biopsied	▪ Encompasses a broad range of parenchymal abnormalities ▪ Ground-glass opacities, centrilobular nodules, mosaic attenuation, traction bronchiectasis, reticular abnormalities, non-emphysematous cysts, and honeycombing

† Notes: Alternative term for combined pulmonary fibrosis and emphysema are airspace enlargement with fibrosis (AEF)
Abbreviations: AEP = acute eosinophilic pneumonia, ARDS = acute respiratory distress syndrome, CPFE = combined pulmonary fibrosis and emphysema, CT = computed tomography, DIP = desquamative interstitial pneumonia, fNSIP = fibrotic nonspecific interstitial pneumonia, HRCT = high-resolution computed tomography, ILA = interstitial lung abnormality, ILD = interstitial lung disease, IPF = idiopathic pulmonary fibrosis, NSIP = nonspecific interstitial pneumonia, PFT = pulmonary function test, PLCH = pulmonary Langerhans cell histiocytosis, RB = respiratory bronchiolitis, RBILD = Respiratory Bronchiolitis-Associated Interstitial Lung Disease, SRIF = smoking-related interstitial fibrosis, UIP = usual interstitial pneumonia