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Smoking-Related Lung Disease

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Smoke from cigarettes and other sources may induce a variety of patterns of lung injury. While smoking related lung diseases, in general, have a better prognosis than many other diffuse lung diseases, they may be a cause of significant symptoms and, in some cases, may even require lung transplantation. On histology, the manifestations of these patterns range from reversible inflammation to irreversible emphysema or fibrosis. High-resolution chest CT plays a critical role in the diagnosis of smoking related lung diseases. It has several roles including (1) helping determine diagnosis, (2) assessing the pattern of injury that is present, (3) evaluating the extent and severity of disease, and (4) determining the response to treatment. The practicing radiologist must have a knowledge of the clinical, pathologic, and imaging features of the differnent patterns of lung injury associated with smoke inhalation.

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Introduction

Cigarette smoke is estimated to be responsible for approximately 1 in 5 deaths in the United States.[1] Much of this mortality is attributable to an increased risk of heart disease, stroke, and lung cancer; however, smoking-related lung diseases (SRLDs) are also a contributor. While smoking is best known for its ability to cause emphysema and chronic bronchitis, it is also associated with a variety of other patterns of diffuse lung disease (DLD) that may also be a source of mortality. In a study by Wasko et al[2] interstitial lung abnormalities (ILAs) were visualized in 8% of smokers on HRCT, and these ILAs have been associated with reduced survival.[3] SRLDs are also important to recognize given their ability to mimic DLDs that are unrelated to smoking. Making an accurate diagnosis in these cases often has a significant impact on treatment and prognosis. The goal of this paper is to describe the clinical, radiologic, and pathologic manifestations of the spectrum of SRLDs.

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Clinical Approach

The key components of the clinical history in any patient with suspected DLD include: (1) inhaled exposures, (2) drug exposures, and (3) manifestations of connective tissue disease. Inhaled exposures that are most closely associated with DLD include organic antigens (eg, birds), inorganic antigens (eg, silica), and smoke. The type and volume of smoke inhaled, including changes over time, are important in determining the likelihood of SRLD as a potential cause of pulmonary symptoms.

While injury due to cigarette smoke inhalation has been studied most extensively, other materials, such as cannabis and electronic cigarettes, are potential perpetrators. Their effects on the lungs, however, have been poorly studied. In a small pathologic series of cannabis smokers, intra-alveolar macrophages, and interstitial fibrosis resembling desquamative interstitial pneumonia was seen.[4] Case reports have identified an association between cannabis and bullous emphysema on imaging.[5] Synthetic cannabis has been shown to manifest as diffuse centrilobular nodules and tree-in-bud opacities on CT, corresponding pathologically to organizing pneumonia with or without diffuse alveolar damage.[6] Patients who stop smoking cigarettes and switch to electronic cigarettes show improvement in the degree of airflow obstruction,[7] however the pathologic and radiographic manifestations of electronic cigarettes have not yet been described. The effects of

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secondhand smoke inhalation are also poorly studied. In one study of asbestos workers,[8] secondhand smoke was associated with ground glass opacity on HRCT, possibly indicative of early RB or DIP.

It is important to note that while many patients with SRLD have pulmonary symptoms, an asymptomatic presentation is also not uncommon. Respiratory bronchiolitis and smoking related interstitial fibrosis are both well documented in asymptomatic patients.[9] The mainstay of treatment of SRLDs is smoking cessation. When inflammation is the predominant finding, smoking cessation may be effective in reversing the injury. Rarely findings may progress even with adherence to smoking cessation. Corticosteroids may also be used in cases resistant to improvement with smoking cessation alone, however their efficacy is poorly validated. In advanced cases of SRLD lung transplantation may be required.

Pathologic Approach

From a pathologic perspective SRLDs result in 3 general lung manifestations: (1) inflammation and cellular infiltration, (2) emphysema, and (3) fibrosis. There are multiple different patterns of injury associated with smoke inhalation each of which may show one or more of these end pathologic results. While these patterns are often described as separate entities, in practice an overlap is common.[10] Many demonstrate inflammation as their earliest manifestation. Inflammation, in turn, results in the induction of repair mechanisms that may eventually induce emphysema and/or fibrosis.

The role of pathology in the multidisciplinary approach of DLD is to determine diagnosis when a combination of clinical and radiographic findings is nonspecific. Given that DLDs can show significant variability in their findings throughout the lungs, surgical lung biopsy is preferred over transbronchial, or transthoracic biopsies. The specific patterns of injury that may be seen in association with smoking are discussed below, however several features on pathology are shared by many of these patterns. Lightly pigmented alveolar macrophages are commonly present in both asymptomatic patients and those with pulmonary symptoms. A bronchiolar accentuation of findings is also a typical feature of many smoking related lung diseases, although this distribution is seen with other inhaled diseases such as hypersensitivity pneumonitis. Emphysema on pathology manifests as airspace enlargement and alveolar septal fragmentation. Fibrosis due to smoking has a distinctive appearance that is different from that of many other fibrotic lung diseases, such as usual interstitial pneumonia (UIP). In UIP, the fibrosis is irregular and heterogeneous with marked architectural distortion. Fibrosis due to smoking, on the other hand, manifests as paucicellular uniform thickening of the alveolar septal walls closely resembling nonspecific interstitial pneumonia.

Radiologic Approach

High-resolution chest computed tomography (HRCT) is a critical part of the multi-disciplinary approach to diagnosis and should be obtained in all cases of suspected DLD. When typical HRCT findings are seen in association with a smoking history, an accurate diagnosis of SRLD can often be made without pathology. There is a wide spectrum of HRCT findings that may be seen with SRLD. The knowledge of the typical HRCT manifestations of each pattern, in addition to the nonsmoking related lung diseases whose findings overlap with those patterns, is critical in making accurate diagnoses.

The key findings of SRLD on HRCT include ground glass opacity, nodules (either ground glass attenuation or solid), emphysema, and fibrosis. In many cases, several of these findings co-exist. Ground glass opacity most commonly corresponds to interstitial inflammation and partial alveolar filling by macrophages. Alternatively, glass opacity may correspond to interstitial fibrosis and, in fact, is a more common manifestation of fibrosis in SRLDs compared to other fibrotic lung diseases. Irregular reticulation, traction bronchiectasis, and honeycombing may be present, but are generally less pronounced in SRLDs. Nodules are typically centrilobular in distribution and reflect the bronchiolar distribution of the immune reaction. Emphysema corresponds to areas of lung destruction.

Patterns of Injury in Smoking-Related Lung Disease

The different patterns of SRLD reflect the heterogeneous relationship between the type of smoke inhaled and the nature of the immune reaction that occurs as a response. The insult due to smoke inhalation results in three separate pathways of lung response: (1) inflammation and cellular infiltration, (2) emphysema (lung destruction), and (3) fibrosis. Regardless of the specific pattern present, the consequence will be one or more of these end results (Fig. 1)

The specific patterns of injury associated with smoke inhalation (Table 1) will be discussed below, with those most closely associated with inflammatory changes presented first followed by those with predominantly irreversible findings. The discussion of each pattern will focus on the following: (1) clinical manifestations, (2) radiology-pathology correlation, (3) differential diagnosis, and (4) natural history and prognosis.

Acute Eosinophilic Pneumonia

Clinical

Greater than 95% of cases of acute eosinophilic pneumonia (AEP) are due to cigarette smoke exposure.[11] The majority of patients have a history of a change in their smoking habits (eg, increased number of cigarettes smoked per day) in the month leading up to the development of symptoms.[12] In contradistinction to other patterns of SRLD, AEP presents with rapidly progressive acute symptoms, resembling acute respiratory distress syndrome. Admission to the intensive care unit is

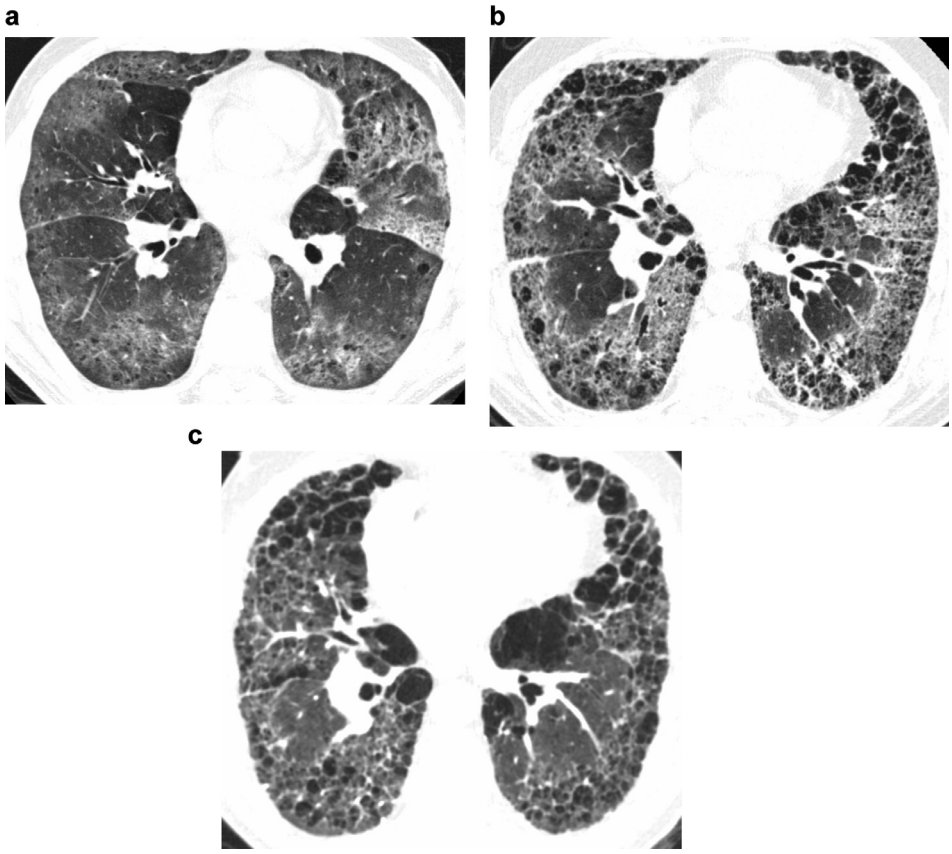

Figure 1 (a-c). Evolution of smoking related lung disease over time. Baseline CT (Fig. 1a) demonstrates peripheral ground glass opacity with scattered cystic lucencies typical of desquamative interstitial pneumonia. Four years later (Fig. b) the cystic lucencies are more extensive and have more discreet walls. While the ground glass persists there is development of reticulation and mild traction bronchiectasis. Another 5 years later (Fig. c) the ground glass has disappeared, and the cystic lucencies and reticulation are the main abnormality. These findings correspond to emphysema and fibrosis.

required in most. As opposed to other eosinophilic lung diseases, a peripheral eosinophilia is only seen in a minority of patients (approximately 30%).

Radiology-Pathology Correlation

Pathology in AEP is essentially diffuse alveolar damage (DAD) with airspace consolidation by macrophages, fibrin, and eosinophils.[13] The HRCT findings resemble DAD from other causes with a combination of extensive bilateral ground glass opacity and smooth interlobular septal thickening ("the crazy-paving" pattern) or consolidation (Fig. 2). Fibrosis and emphysema are not characteristic features of AEP.

Differential Diagnosis

The clinical and radiographic features of AEP are relatively nonspecific and overlap with other causes of acute pulmonary symptoms. Diagnosis is further confounded by the relatively low rate of peripheral eosinophilia. Making a diagnosis of AEP necessitates a high suspicion based upon the smoking history. Bronchoalveolar lavage, in search for tissue eosinophils, may be helpful in patients with a history of smoking and diffuse alveolar damage of unknown etiology. From a radiologic perspective the findings of AEP on HRCT are indistinguishable from pulmonary edema, certain infections (eg, viral), diffuse alveolar damage, and diffuse alveolar hemorrhage.

Natural History and Treatment

In distinction to other causes of diffuse alveolar damage, AEP is a pattern that demonstrates rapid improvement after corticosteroid treatment, thus a diagnosis of AEP has a significant impact on treatment. Resolution of chest radiographic abnormalities is seen in about 85% of patients within 7 days.[11]

Langerhan's Cell Histiocytosis

Clinical

Langerhan's Cell Histiocytosis (LCH) is a rare manifestation of SRLD with distinctive pathologic and imaging findings. In children, LCH is a systemic disorder unrelated to smoking, however in adults it is predominantly a SRLD. In a study of 102 adults with Langerhans cell histiocytosis 68% were current smokers and 27% were former smokers. Extrapulmonary involvement in this study was uncommon, present in only 17%. Patients with LCH may present with symptoms of dyspnea or pneumothorax. In a study of 122 adults with LCH, 16% developed a pneumothorax.[14] However, in about 15% of patients, LCH is discovered as an incidental finding.[15]

Table 1 Patterns of Injury Due to Smoke Inhalation

Pattern	Clinical	Pathologic	HRCT
Acute Eosinophilic Pneumonia	- Acute onset - Resembles acute respiratory distress syndrome - Peripheral eosinophilia in only 30% - Rapid response to corticosteroids	- Diffuse alveolar damage - Airspace consolidation by macrophages, fibrin, and eosinophils	- Ground glass opacity and interlobular septal thickening (eg, "crazy paving") and/or consolidation - Diffuse or symmetric distribution
Langerhans Cell Histiocytosis	- Children: systemic disorder unrelated to smoking - Adults: smoking related lung disease, usually isolated to lungs - May present with dyspnea or pneumothorax; sometimes asymptomatic	- Collections of histiocytes around bronchioles - Progressive airway dilation within nodules - Irregular emphysema surrounded by scar	- Soft tissue attenuation centrilobular nodules - "Cavitation" within nodules - Irregular cysts - Sparing of lung bases
Respiratory Bronchiolitis (RB)	- Spectrum with DIP - Present in all smokers on pathology - May be a cause of dyspnea but is more commonly asymptomatic	- Intra-alveolar macrophages - Alveolar septal wall thickening by inflammation or fibrosis - Peribronchiolar distribution	- Centrilobular ground glass nodules - Upper lobe distribution
Desquamative Interstitial Pneumonia (DIP)	- Spectrum with RB but a more generalized reaction - Symptoms often more pronounced than with RB	- Intra-alveolar macrophages - Alveolar septal wall thickening by inflammation or fibrosis - More diffuse distribution than with RB	- Basilar ground glass opacity - Cystic lucencies - Fibrosis, although ground glass opacity is often a manifestation of fibrosis in DIP
Smoking-Related Interstitial Fibrosis	- Often an incidental finding seen on pathologic specimens in patients without symptoms	- Centrilobular and subpleural alveolar septal wall thickening by fibrosis - Associated respiratory bronchiolitis and emphysema	- HRCT often normal - When findings are present they overlap with RB and DIP
Idiopathic Pulmonary Fibrosis (IPF)	- 60%-70% of IPF patient are smokers - Progressive disease with poor prognosis - Acute exacerbation may occur	- Microscopic honeycombing - Fibroblastic foci - Subpleural fibrosis	- Fibrosis with honeycombing - Subpleural and basilar distribution
Emphysema	- Irreversible consequence of chronic smoke inhalation - Represents lung destruction - Wide range of severity	- Airspace enlargement - Alveolar septal fragmentation - Simplification of lung architecture	- Focal air-attenuation lucencies without a wall - May appear to have a wall when emphysema is surrounded by fibrosis

Radiology-Pathology Correlation

Pathologically, LCH is characterized by bronchiolocentric stellate nodules composed of Langerhans cell histiocytes and eosinophils. On HRCT (Fig. 3) this corresponds to centrilobular nodules, often of soft tissue attenuation. Over time, these collections of histiocytes cause destruction of the centrilobular bronchiolar wall and focal dilation of the airway.[16] On HRCT this will appear as air-attenuation lucencies at the center of the solid nodules, resembling cavitation. Progressive bronchiolar dilation and lung destruction eventually results in emphysema surround by fibrosis, manifesting as coalescing irregularly shaped cysts on HRCT.[17] These findings predominate in the mid to upper lungs, sparing the costophrenic angles.

Differential Diagnosis

LCH, RB and DIP often co-exist, thus overlapping clinical, pathologic, and imaging findings may be present. The differential diagnosis of LCH is somewhat different than other SRLDs because of its unique imaging findings. The predominantly solid nodules of LCH may be confused with metastatic malignancy, certain infections (eg, fungal or mycobacterial organisms) or tracheobronchial papillomatosis. When cysts are the predominant finding, lymphangioleiomyomatosis (LAM) is often considered. LAM is distinguished from LCH by a lack of nodules, and cysts that are round and involve the lung bases.

Natural History and Treatment

The treatment for LCH is smoking cessation and, if necessary, corticosteroid treatment. The prognosis is generally

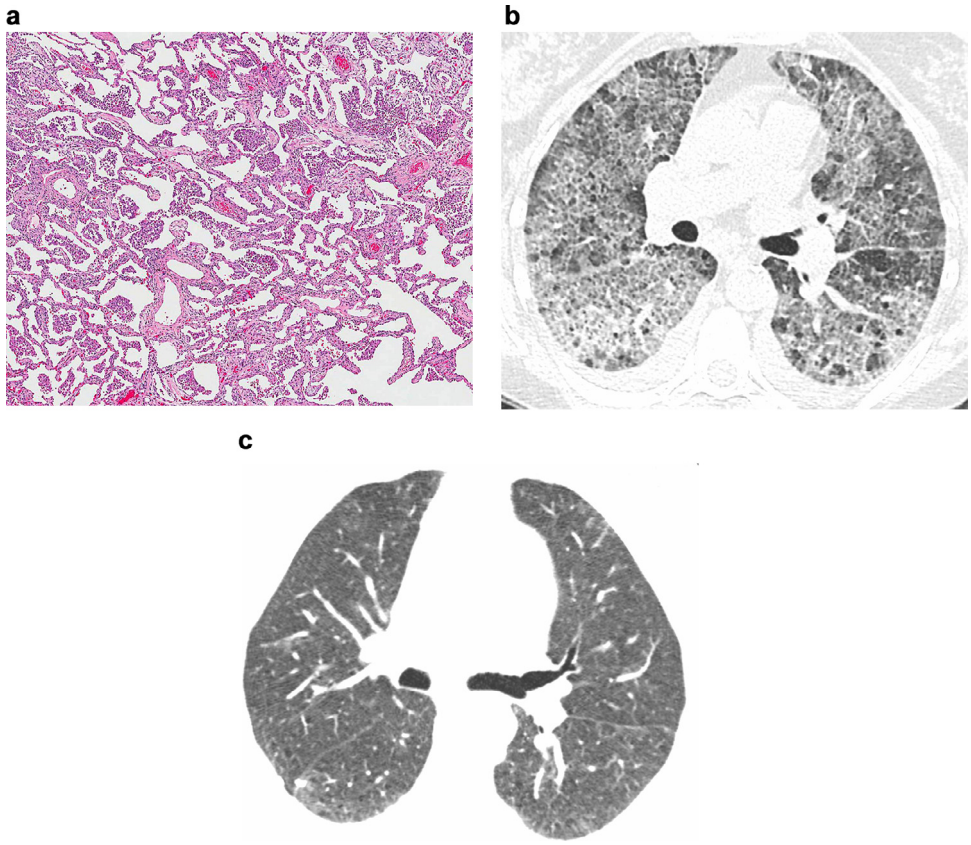

Figure 2 (a-c). Acute eosinophilic pneumonia. Surgical biopsy (Fig. 2a) shows alveolar filling by macrophages and eosinophils, and mild alveolar septal thickening by edema and early fibrosis. On HRCT (Fig. 2b) ground glass opacity and interlobular septal thickening is present in a patient who recently increased the number of cigarettes smoked per day. Three months after treatment with corticosteroids (Fig. 2c) there is near resolution of the abnormalities.

quite good compared to other DLDs. In a study of 102 adults with LCH, the median survival was 12.5 years.[15] Paradoxical recurrence after smoking cessation and regression while continuing smoking have been reported.[18] In a study of serial HRCTs in 21 patients with LCH, there was a reduction in the percentage of CTs with micronodules (initial: 86%, follow-up: 43%) and thick-walled cysts (initial: 48%, follow-up: 24%) over time.[19] Findings that worsened on interval imaging included: thinned walled cysts (initial: 62%, follow-up: 67%) and emphysema (initial: 24%, follow-up: 43%).

Respiratory Bronchiolitis and Desquamative Interstitial Pneumonia

Clinical

Respiratory bronchiolitis (RB) and desquamative interstitial pneumonia (DIP) are thought to represent a spectrum of disease with significant clinical, radiologic, and pathologic overlap.[20] They are both closely associated with a history of smoking, although in one study[21] 40% of patients with DIP were nonsmokers. Both may also be seen as a minor secondary pattern in association with another DLD, such as idiopathic pulmonary fibrosis in which case they may simply be a marker of smoke exposure. Also, RB and DIP may be detected as an incidental radiographic or pathologic finding in asymptomatic patients. For this reason, a diagnosis of RB or DIP as a cause of pulmonary symptoms should only be made when other causes of DLD are excluded.

Radiology-Pathology Correlation

RB and DIP are characterized by alveolar filling by macrophages in either a peribronchiolar or diffuse distribution respectively. These may be associated with inflammation or fibrosis of the alveolar septal walls. While the typical HRCT findings of RB and DIP will be discussed separately, it is important to remember that they exist on a spectrum and thus overlap of radiologic findings is common.[20]

In a study of 21 smokers[22] with respiratory bronchiolitis, the most common HRCT features included central airway thickening in 90%, centrilobular nodules in 71%, and ground glass opacity in 67% of patients. As both airway thickening and ground glass opacity are nonspecific, the most suggestive feature of RB is centrilobular nodules of ground glass attenuation (Fig. 4). This finding corresponds pathologically to the patchy alveolar filling by smoker's macrophages, interstitial inflammation, and cellular infiltration adjacent to the centrilobular bronchiole.

DIP classically manifests on HRCT as ground glass opacities that have a basilar predominance.[23,24] These ground glass opacities correspond pathologically to uniform thickening of the interstitium by inflammation or fibrosis, and

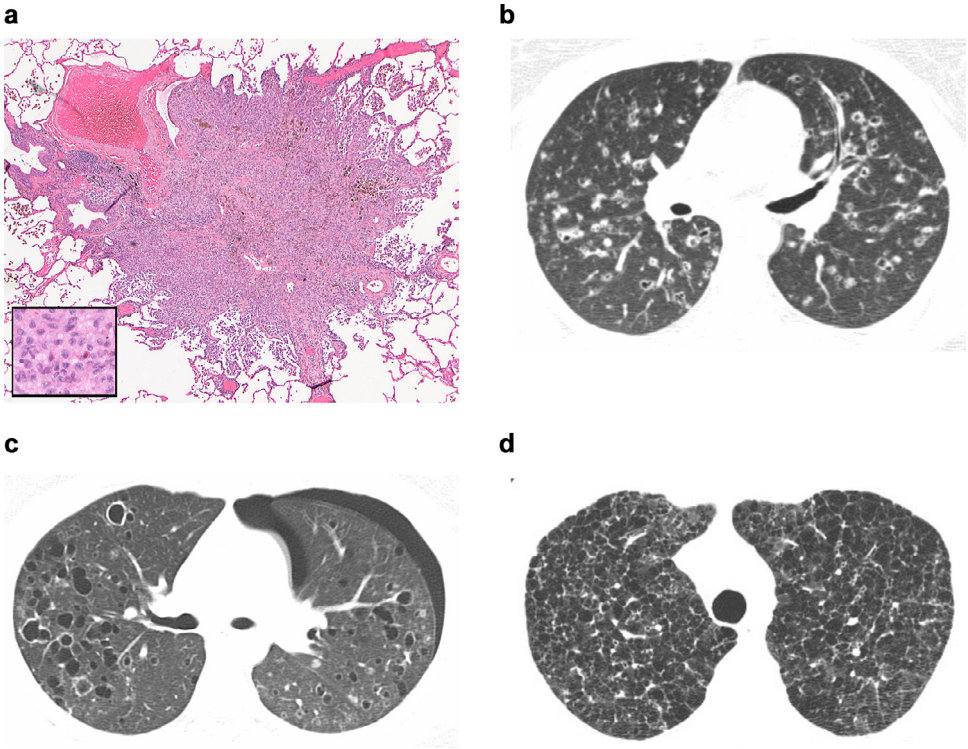

Figure 3 (a-d). Langerhans cell histiocytosis (LCH). Surgical biopsy (Fig. 3a) shows a stellate nodule composed of Langerhans cell histiocytes. On high magnification, the Langerhans cells show characteristic reniform nuclei with nuclear contour irregularities. Scattered eosinophils are present. On HRCT in 1 patient (Fig. 3b) soft tissue, attenuation centrilobular nodules are present, many of which have air attenuation lucencies at their centers. In another patient presenting with a pneumothorax (Fig. 3c) there are irregular cysts with thick and thin walls, in addition to a few nodules. In a third patient (Fig. 3d) extensive cysts that nearly replace the normal lung parenchyma are present. These may be difficult to distinguish from extensive emphysema.

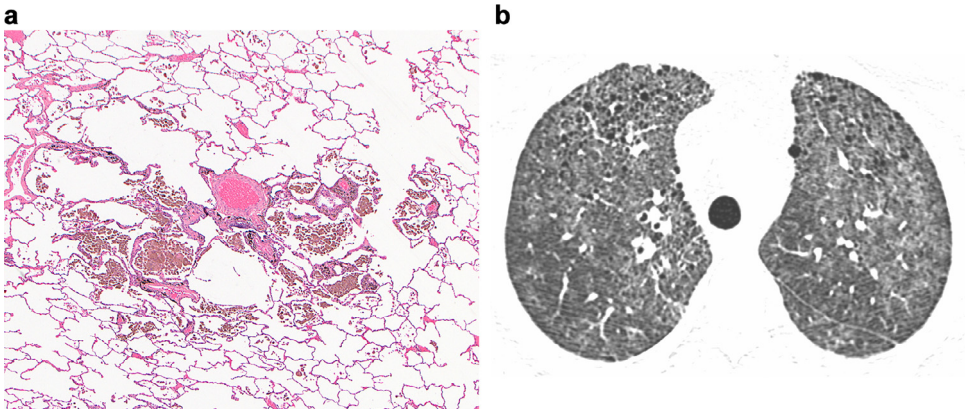

Figure 4 (a-b). Respiratory bronchiolitis (RB). Surgical biopsy (Fig. 4a) shows peribronchiolar alveolar filling by lightly-pigmented pulmonary macrophages. Airspace enlargement of centriacinar emphysema is present. On HRCT (Fig. 4b) these pathologic findings correlate with centrilobular nodules of ground glass attenuation. Also note the presence of emphysema.

patchy filling of the alveolar spaces by pigmented macrophages. While ground glass opacity is the most common finding of DIP, seen in nearly 100% of patients, fibrosis and cystic lucencies may also be present (Fig. 5). The cystic lucencies have a different morphology than honeycombing and may be representative of emphysema or dilated alveolar ducts and bronchioles.[24] On pathology, fibrosis in DIP closely resembles that of NSIP with uniform thickening of the alveolar septal walls by fibrosis and relatively preserved lung architecture. This explains the relatively high occurrence of ground glass opacity as a predominant finding in both fibrotic DIP and NSIP. Irregular reticulation, traction

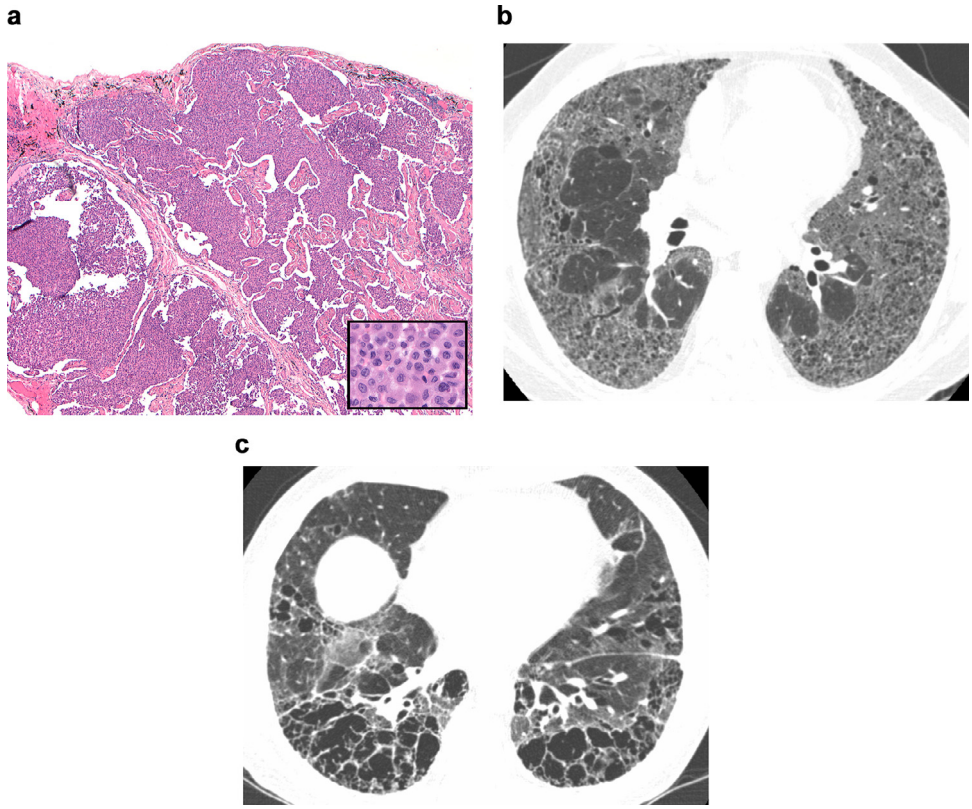

Figure 5 (a-c). Desquamative interstitial pneumonia (DIP). Surgical biopsy (Fig. 5a) shows alveolar filling by macrophages and thickening of the alveolar septa by fibrosis. On HRCT (Fig. 5b) there is a basilar distribution of ground glass opacity and associated with cystic lucencies. In another patient with more advanced DIP (Fig. 5c) there are extensive subpleural air attenuation cystic lucencies without ground glass opacity. This appearance could be confused with honeycombing, however the thin walls, irregular shapes, and sparing of the immediate subpleural interstitium in some regions are typical of DIP.

bronchiectasis, and honeycombing may be seen with DIP, however they are typically less prominent than with other fibrotic lung diseases.

Differential Diagnosis

The diagnosis of RB or DIP is often made by the presence of typical HRCT findings and an appropriate smoking history. The differential diagnosis of these patterns depends upon the predominant features present at the time of detection. In cases of RB presenting with centrilobular ground glass nodules, hypersensitivity pneumonitis (HP) is often the main diagnostic consideration.[25] A history of exposure to bird or mold antigens in conjunction with a lymphocytosis on bronchoalveolar lavage are suggestive of HP. Smoking is relatively protective against the development of HP.

As discussed above, DIP and NSIP show significant overlap in their pathologic and HRCT findings. On HRCT both patterns present with basilar predominant ground glass opacity. The presence of subpleural sparing on imaging strongly suggests NSIP. The cystic lucencies of fibrotic DIP may resemble honeycombing in which case usual interstitial pneumonia (UIP) is often also considered. The morphology of these cysts differs from honeycombing in that they have thinner walls, irregular shapes, (ie, not round) and often spare the subpleural lung. The presence of ground glass opacity and the relative paucity of honeycombing also help distinguish DIP from UIP.[26]

Natural History and Treatment

While RB has been traditionally thought of as having a 5-year survival approaching 100%, a more recent investigation by Portnoy et al[27] estimated that survival in symptomatic RB was at approximately 75% after 7 years. Interestingly, only 28% of patients in this study showed clinical improvement over time suggesting that in most patients the disease was predominantly irreversible. In the study by Ryu et al[28] the 3-year survival of DIP was 74%. Symptomatic improvement and a decrease in HRCT abnormalities were also only seen in a minority of patients (24% and 33%, respectively). While patients with RB and DIP who adhere to smoking cessation may show a decrease in the nodules and ground glass opacity on HRCT,[29] residual ground glass opacity often persists, likely reflecting microscopic areas of fibrosis. In a study of the serial HRCT follow-up of DIP patients, Hartman and colleagues[30] discovered that >90% of patients with DIP had residual ground glass opacity on interval follow-up. Additionally, 20% of DIP patients developed new reticulation and/or honeycombing over time. In patients who continue to smoke, the severity of ground glass opacity, and emphysema on HRCT may increase over time,[31] and patients may

develop cystic lucencies or honeycombing.[32] The cystic lucencies, in these cases, may represent areas of emphysema surrounded by fibrosis.

Smoking-Related Interstitial Fibrosis and Airspace Enlargement with Fibrosis

Clinical

Smoking may induce a reaction that results in lung fibrosis without a clear preceding inflammatory stage. Smoking-related interstitial fibrosis (SRIF),[9] airspace enlargement with fibrosis,[33] and respiratory bronchiolitis with fibrosis[34] are pathologic terms given to this entity. These patterns have primarily been described as incidental findings on histology obtained in patients in whom there was not a suspicion for DLD. In the study by Kawabata et al,[33] 18% of moderate smokers had this histologic finding on lobectomy specimens.

Radiology-Pathology Correlation

Typical histology includes centrilobular and subpleural alveolar septal thickening by fibrosis associated with respiratory bronchiolitis and emphysema. It is likely that these patterns are simply the sequela of prior RB or DIP in which case the inflammatory precursor was missed. The HRCTs (Fig. 6) in these patients may be normal or the findings may overlap with RB and DIP. In the series by Yousem et al, 8 of 9 patients with SRIF demonstrated bilateral micronodules on CT.[34] Chae et al[35] compared the HRCT findings of SRIF and usual interstitial pneumonia (UIP). They found that findings associated with SRIF included "honeycombing" that spared the subpleural lung, lack of honeycombing in the upper lobes, and emphysema adjacent to areas of honeycombing. These descriptions, in some respects, resemble cases of fibrotic DIP. Reddy et al[36] found that the HRCT findings of SRIF included mid to upper lung emphysema associated with mild reticulation and/or ground glass opacity.

Differential Diagnosis

The differential diagnosis of SRIF is more of a pathological problem than a clinical or radiologic one. A pathologist must distinguish SRIF from more ominous patterns such as usual interstitial pneumonia. From a clinical perspective, most patients with SRIF are asymptomatic, although studies evaluating the long-term progression of SRIF into a clinically significant disease have not been performed. On imaging, the HRCT findings of SRIF overlap with RB and DIP. Since these patterns may all represent a spectrum of the same process, their distinction may not be important.

Natural History and Treatment

While the long-term prognosis of patients with SRIF is unknown, the fact that many patients are asymptomatic suggests that this may be a relatively indolent pattern. In the study by Yousem et al[34] 78% of patients were stable over time and

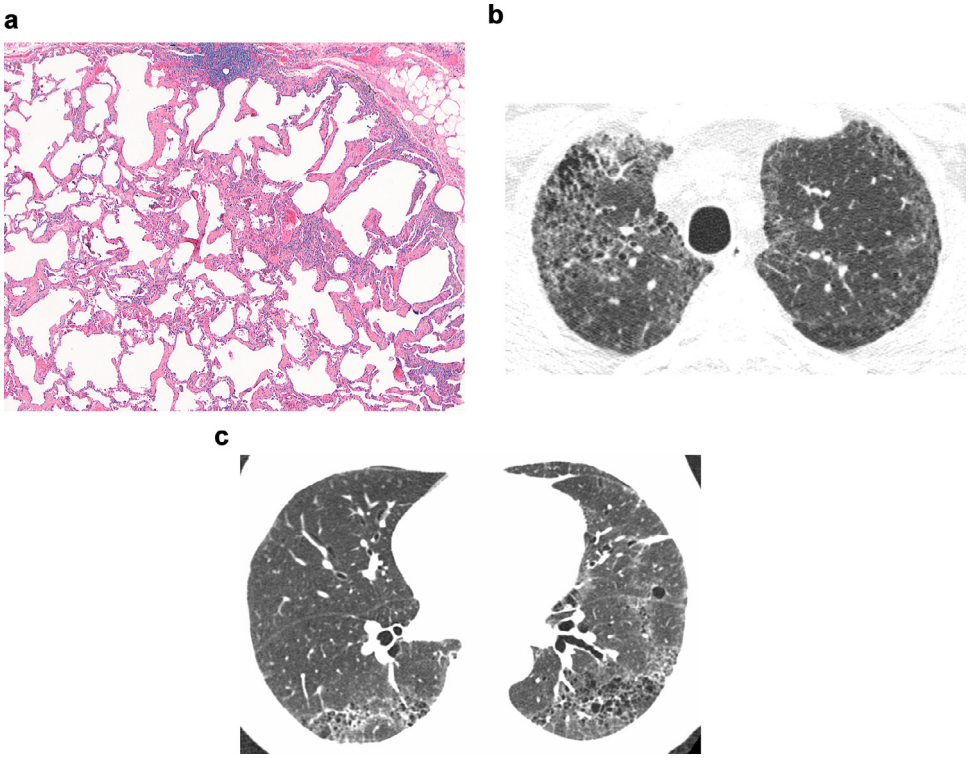

Figure 6 (a-c). Smoking related interstitial fibrosis (SRIF). Surgical biopsy (Fig. 6a) shows uniform subpleural alveolar septal thickening by dense hyalinized collagen. On HRCT (Fig. 6b) mild upper lung ground glass opacity, centrilobular ground glass nodules, and emphysema in SRIF resembles respiratory bronchiolitis. In another patient with SRIF (Fig. 6c) peripheral ground glass opacity, reticulation, and cystic lucencies resemble desquamative interstitial pneumonia.

12% were slowly progressive over a median 3.2 year period. Follow-up of the patients in the study by Katzenstein et al[9] also demonstrated an indolent course in most patients.

Idiopathic Pulmonary Fibrosis

Clinical

Approximately 60%-70% of patients with idiopathic pulmonary fibrosis (IPF) are current or former smokers.[37,38] The exact mechanism of this interaction is not clear. Smoke may, in part, be directly responsible for the injury associated with lung fibrosis or it may sensitize the lung to injury. Regardless, IPF differs from other smoking related lung diseases in that it is a process characterized entirely by fibrosis without inflammation.

Given the high percentage of smokers amongst IPF patients, lung fibrosis, and emphysema may coexist. This combination of findings is termed combined pulmonary fibrosis and emphysema (CPFE). CPFE is not a diagnosis per se, but is simply a combination of emphysema, and a fibrotic lung disease. That fibrotic lung disease is often IPF, but not always. In a study of 10 patients with CPFE,[39] 80% had usual interstitial pneumonia whereas 20% had DIP. Given the different prognosis and treatment of DIP compared to IPF, a confident diagnosis of the underlying fibrotic lung disease in patients with CPFE is important.

Radiology-Pathology Correlation

The imaging findings of IPF are usually easily distinguishable from other patterns of injury in SRLD with the exception of DIP. Both IPF and DIP may show a basilar and subpleural distribution of fibrosis. The emphysema or cystic lucencies of DIP may resemble the honeycombing of IPF. DIP has a greater preponderance of ground glass opacity, and less traction bronchiectasis and irregular reticulation. The cystic lucencies of DIP differ from honeycombing in that they have irregular shapes (ie, are not round), have thin walls, and do not extend to the subpleural lung. From a clinical perspective, DIP tends to progress much more slowly than IPF.

Natural History and Treatment

In distinction to most other SRLDs, the mortality of IPF is high with a mean survival of approximately 3-4 years after diagnosis.[40] Serial HRCTs in IPF patients demonstrate worsening of the extent of fibrosis in about 90% of patients over a 4-year follow-up period.[41] Acute exacerbation, manifesting as rapidly worsening clinical symptoms and new ground glass opacity on HRCT, is also more common with IPF than other SRLDs. Pirfenidone and nintedanib are unique treatments for IPF that may slow the progression of fibrosis.[42,43]

Emphysema

Clinical

A comprehensive discussion of emphysema is beyond the scope of this paper; however, it is important to mention given that it is the end result of many of the other patterns of SRLD. Emphysema reflects an irreversible consequence of smoke inhalation characterized by lung destruction from chronic inflammation and cellular infiltration. Clinically it may result in profound airway obstruction and dyspnea, or it may be detected at an early, subclinical stage. It is often seen in association with the other patterns described above.

Radiology-Pathology Correlation

On pathology, emphysema manifests as airspace enlargement and destruction of the alveolar septal walls, resulting in areas of lung with a simplified architecture. A centrilobular distribution of emphysema is most common, reflecting the airway-centered nature of the injury. On HRCT this manifests as focal, air-attenuation lucencies without a wall predominating in the central portions of the upper lungs. When emphysema is surrounded by fibrosis, as seen in DIP, it may appear to have a wall at its periphery.

It is important to note that uniform distribution of emphysema throughout the lungs may result in clinically significant abnormalities that are not detectable on HRCT. Quantitative lung imaging is a technique that may improve the HRCT sensitivity for emphysema and may also provide an assessment of the extent and severity of disease. Additionally, quantitative lung imaging may be useful in the serial evaluation of emphysema over time. However, the clinical utility of these techniques is still to be determined.

Differential Diagnosis

Centrilobular emphysema has a characteristic appearance on HRCT. Distinction should be made between emphysema and other air attenuation abnormalities. Cysts are air-attenuation lucencies that have a thin, but discreet wall at their periphery, although emphysema surrounded by fibrosis may appear to have a wall. Bronchiectasis has a tubular configuration corresponding to dilated airways. Honeycombing cysts are clustered, have thick walls, and involve the subpleural lung.

Natural History and Treatment

As emphysema is an irreversible finding, treatment focuses on preventing further progression of disease and ameliorating symptoms. As with other patterns of SRLD, smoking cessation forms the cornerstone of treatment. Beta-agonists are used to temporarily relieve airways obstruction and corticosteroids to reduce airways inflammation. Even in patients who stop smoking, progression of emphysema may occur. Quantitative lung imaging may aid in characterizing this progression and may be more sensitive than other measures of lung function.[44]

Conclusion

The effects of smoking on the lungs are varied and result in a variety of patterns of injury characterized by either potentially reversible inflammatory changes or irreversible changes of emphysema or fibrosis. Most SRLDs have a good prognosis, and an asymptomatic presentation is not uncommon. HRCT is important in the detection and characterization of SRLDs, and in their distinction from other DLDs. This distinction is critical in the treatment of patients, particularly in terms of the need for exposure removal, and immunosuppressive therapy.

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