Smoking-Related Interstitial Lung Diseases

Robert Vassallo, MD[a,b], Jay H. Ryu, MD[a,*]

KEYWORDS

- Smoking • Interstitial lung disease
- Respiratory bronchiolitis
- Desquamative interstitial pneumonia • Fibrosis
- Pulmonary Langerhans cell histiocytosis
- Acute eosinophilic pneumonia

Cigarette smoke is a complex mixture of more than 4000 chemicals, many of which exert toxic effects on cellular function. In addition to chronic obstructive pulmonary disease (COPD) and cancer, cigarette smokers may develop certain diffuse interstitial and bronchiolar disorders (**Box 1**, **Table 1**).[1–4] These diffuse lung diseases are referred to as smoking-related interstitial lung diseases (ILDs), a term that recognizes the suspected causal association with cigarette smoking. Novel insights regarding the relationship between smoking and ILD are highlighted in this review.

SMOKING AND ILD

Cigarette smoking is now widely accepted as the primary cause of certain ILDs, namely, respiratory bronchiolitis–associated ILD (RB-ILD), desquamative interstitial pneumonia (DIP), and pulmonary Langerhans cell histiocytosis (PLCH).[1–5] Cigarette smoking is also a risk factor for the development of idiopathic pulmonary fibrosis (IPF)[14] and rheumatoid arthritis (RA)-associated ILD[15,24] and has been reported to cause some cases of acute eosinophilic pneumonia (AEP)[25] and pulmonary hemorrhage syndromes. Paradoxically, cigarette smoking may confer protection from developing some other ILDs such as hypersensitivity pneumonitis (HP).[26] The authors recently described a classification scheme (see **Box 1**) outlining these subgroups and their relationship with smoking.[27] This classification illustrates the highly complex effects of smoking on lung parenchyma and ILDs.

The group 1 diseases (see **Box 1**) include the 3 diffuse lung diseases widely regarded as true smoking-related ILDs. This designation is supported by several lines of clinical, epidemiologic, and investigative evidence showing a direct role for cigarette smoking as witnessed in the temporal relationship to disease onset and progression, resolution on smoking cessation, and recurrence on resumption of smoking.[6,28–31] Several case series have reported a history of smoking in the overwhelming majority of patients with group 1 diseases, with the prevalence being highest in RB-ILD,[4,32] followed by PLCH,[2,5] and least common in DIP.[4,7] The reported coexistence of all 3 lesions in the same patient,[6] the potential for disease remission with smoking cessation,[4] the recurrence of disease in transplanted lungs,[33,34] and the description of analogous lesions in mice exposed to high doses of cigarette smoke[29] provide support to the designation of RB-ILD, DIP, and PLCH as smoking-induced ILDs.

Supported by a Flight Attendant Medical Research Institute (FAMRI) award to R.V.
The authors have no conflict of interest.
All authors have directly contributed to the content of this manuscript and reviewed the final version.
[a] Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Gonda 18 South, 200 First Street Southwest, Rochester, MN 55905, USA
[b] Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN 55905, USA
* Corresponding author.
E-mail address: ryu.jay@mayo.edu

Clin Chest Med 33 (2012) 165–178
doi:10.1016/j.ccm.2011.11.004

Box 1
Proposed classification of smoking-related ILDs

Group 1: chronic ILDs that are very likely caused by cigarette smoking[4–8]

- Respiratory bronchiolitis–associated ILD
- Desquamative interstitial pneumonia
- Adult pulmonary Langerhans cell histiocytosis

Group 2: acute ILDs that may be precipitated by cigarette smoking[9–13]

- Acute eosinophilic pneumonia
- Pulmonary hemorrhage syndromes

Group 3: ILDs that are statistically more prevalent in smokers[14–18]

- Idiopathic pulmonary fibrosis
- Rheumatoid arthritis–associated ILD

Group 4: ILDs that are less prevalent in smokers[19–23]

- Hypersensitivity pneumonitis
- Sarcoidosis

Diseases allocated to group 2 (see **Box 1**) differ because the association with cigarette smoking is less robust than that for group 1 diseases. Cigarette smoking, particularly during the relatively early phase of initiation of smoking, seems to be an important precipitating factor in some but not all cases of group 2 diseases. The most relevant conditions in this category include AEP and certain pulmonary hemorrhage syndromes.[9–11,25,35] AEP deserves particular attention because several recent studies have implicated recent-onset exposure to cigarette smoke as a principal inducer of this disease in some patients diagnosed to have this disorder.[10,12,35–37] Of particular interest is the response of certain subjects with resolved AEP to a rechallenge with cigarette smoke exposure that triggers peripheral eosinophilia and other associated pathophysiologic abnormalities suggesting exposure to cigarette smoke to induce certain responses relevant to the development of acute diffuse lung disease in susceptible hosts.[10]

Diseases included in group 3 (see **Box 1**) are chronic diffuse lung diseases that are statistically more likely to develop in cigarette smokers.[16,17] For instance, cigarette smoking is known to increase the relative risk of RA-associated ILD, possibly by triggering RA-specific immune reactions to citrullinated proteins.[16,18,24] Similarly, smokers have a higher risk of developing IPF than nonsmokers.[17] The precise significance of these observations has been a topic of substantial debate, but there is limited evidence that smoking itself is directly fibrogenic to the lung.[38] It is not appropriate to consider smoking as an inducer of these diseases, but rather a disease modifier or potentially a cofactor that facilitates the development of profibrotic responses that lead to these diffuse fibrotic lung diseases.

Table 1
Key characteristics of group 1 chronic smoking–related diffuse lung diseases

	RB-ILD	DIP	PLCH
Association with Cigarette Smoking	95%	60%–90%	95%–97%
Clinical Features	Chronic cough and dyspnea, inspiratory crackles	Chronic cough and dyspnea, inspiratory crackles	Chronic cough and dyspnea. Pneumothorax in 15%
High-Resolution Computed Tomographic Findings	Centrilobular nodules and ground-glass opacities	Ground-glass and reticular opacities	Peribronchiolar nodules, cavitated nodules, and cysts with relative sparing of lung bases
Key Histologic Findings	Pigment-laden macrophages in the respiratory bronchioles and alveolar ducts	Diffuse alveolar filling with pigment-laden macrophages	Bronchiolocentric nodules, stellate lesions, CD1a-positive Langerhans cells
Response to Corticosteroids	Modest, variable	Modest, variable	Modest, variable

Abbreviations: DIP, desquamative interstitial pneumonia; PLCH, pulmonary Langerhans cell histiocytosis; RB-ILD, respiratory bronchiolitis–associated interstitial lung disease.

The fourth and final group consists of diseases that are less prevalent in smokers than nonsmokers and includes sarcoidosis and HP.[19–22] Cigarette smoking seems to provide certain protective effects that diminish the potential development of these granulomatous inflammatory lung diseases, possibly by inhibiting certain immunologic responses in the lung that are required for granuloma formation or the development of T-helper subtype 1 (T_H1)-polarized immune responses following exposure to inhaled antigens.[39,40] Epidemiologic studies demonstrate that levels of circulating IgG antibodies to pigeon antigens are higher among nonsmokers than smokers.[41] A similar study in farmers showed that nonsmokers and previous smokers had a higher prevalence of serum precipitin levels to various farmer's lung antigens compared with current smokers.[42] Lung macrophages from cigarette smokers also have lower levels of costimulatory molecules than controls.[40] Because costimulatory molecules play a critical role in shaping the immune response to inhaled antigens, it is possible that smokers are hyporesponsive to inhaled antigens by virtue of diminished antigen-presenting capacity in the lung. Cigarette smoking and nicotine have also been demonstrated to inhibit the production of the potent T_H1-polarizing cytokine interleukin (IL) 12.[39] It is conceivable that the diminished capacity of smokers' macrophages and dendritic cells to generate IL-12 may impede the development of hypersensitivity response to inhaled antigens and granuloma formation in the context of sarcoidosis. The observation that smoking is associated with a lower prevalence of sarcoidosis and HP should not be construed as an indication to promote smoking in patients with these diseases. On the contrary, the insight gained from dissecting mechanisms by which smoking suppresses T_H1 immunity, an essential driver of the immunopathogenic processes that characterize these diffuse lung diseases, is also relevant to the pathogenesis of smoking-related lung cancer and airway diseases, diseases that are more prevalent in smokers partly because of impaired T_H1 immunity.

The fact that some cases of RB-ILD or DIP may be induced by factors other than cigarette smoke exposure and that some patients with PLCH are nonsmokers had been interpreted as implying that these disease do not necessarily represent specific smoking-induced lung diseases. However, it is well recognized that several specific histopathologic entities can be induced by heterogeneous etiologies, potentially a reflection that the lung has only a limited number of ways of responding to various insults. For example, the lesion of usual interstitial pneumonia (UIP) may be induced by asbestos exposure and may be seen in patients with chronic HP, as well as in the context of autoimmune diseases such as RA-associated ILD.[43,44] Cigarette smoking is the most well-defined etiologic factor associated with the development of RB-ILD, DIP, and PLCH; however, the histopathologic lesions of RB, DIP, and PLCH do not exclusively occur in smokers and may occasionally be idiopathic or encountered in the context of other exposures or causes.[5,7,8]

Defining the relationship between smoking and specific ILDs has important clinical implications. Smoking cessation is imperative for all the diseases listed under groups 1 to 3 in **Box 1**. Physicians use aggressive tobacco cessation strategies in these patients, and, for these patients, there is a low threshold for referral to nicotine dependence counselors. It is the authors' practice to explicitly refer to diseases in group 1 as smoking induced to underscore the importance of smoking cessation and encourage removal of all tobacco products from the vicinity of the patient, including second-hand tobacco smoke exposure. Similarly, all current smokers with diseases in groups 2 and 3 should be counseled regarding the emerging and compelling data implicating a direct pathogenic role for cigarette smoke exposure as a potential inducer or cofactor in disease induction and progression. Methods that should be considered in smoking cessation therapy include counseling and behavior therapy, nicotine replacement therapy, and pharmacotherapy, including the use of bupropion, varenicline, and clonidine in selected patients.[45]

MECHANISMS BY WHICH TOBACCO SMOKE MAY PROMOTE ILD

Even in smokers without clinically detectable lung disease, cigarette smoking induces inflammatory cell recruitment, consisting primarily of macrophages, neutrophils, and Langerhans cells (a subtype of the myeloid dendritic cell family expressing surface CD1a receptors), to small airways.[46,47] Although all smokers have some degree of inflammation in the airways, only a minority develop clinically significant diffuse lung disease. The relative rarity of smoking-related ILDs compared with the overall prevalence of cigarette smoking suggests that cigarette smoke is not the only factor responsible for the induction of these diseases and implies that additional factors (endogenous such as genetic factors or exogenous such as infectious pathogens or allergens) are required for the induction of disease.

A characteristic morphologic feature of all group 1 smoking-related ILDs is prominent bronchiolar inflammation.[6,48–50] In addition, group 1 diseases demonstrate increased macrophages in

the interstitium and alveolar spaces.[48,49,51] Pigmented macrophage accumulation in small airways, interstitium, and distal air spaces is a key feature of many smoking-related ILDs. Specific mechanisms by which exaggerated macrophage accumulation occurs in group 1 diseases are not fully defined but likely involve exaggerated generation of macrophage recruiting and differentiating factors by airway epithelial cells, enhanced macrophage survival locally, and/or diminished apoptosis of recruited macrophages.[52] In these patients, lung epithelial cells have been demonstrated to aberrantly produce excessive granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine that provides proliferative and activation signals to both macrophages and dendritic cells.[53,54] Cigarette smoke extracts have also been shown to induce transforming growth factor β (TGF-β) production by lung epithelial cells, a cytokine that is involved in Langerhans cell development, immune modulation, and fibrogenic responses in the airways.[55]

Cigarette smoking induces several abnormalities in immune and other lung cells that are likely relevant to the pathogenesis of smoking-related ILDs.[39,56,57] Certain constituents in cigarette smoke are known to activate epithelial cells, macrophages, neutrophils, and dendritic cells in vitro, promoting generation of chemokines and cytokines that lead to inflammation by promoting immune cell recruitment.[58,59] It is reasonable to speculate that smokers in whom ILD develops have an amplified inflammatory cascade associated with activation of multiple immune cell types that promote a vicious cycle of inflammatory cell recruitment. Whether failure of endogenous antiinflammatory mechanisms or additional exogenous insults such as viral infections have a role in promoting smoking-related ILDs is unknown but should be an important area of future research.

RB-ILD

Niewoehner and colleagues[60] described RB as a histopathologic finding of pigmented macrophage accumulation centering on respiratory bronchioles and neighboring alveoli, a finding that was ubiquitous in cigarette smokers. Subsequent case series described similar findings on lung biopsy specimens from cigarette smokers.[1,6,8] RB can thus be considered a histologic marker of smoking and must be distinguished from RB-ILD, a term coined by Myers and colleagues[50] to recognize the clinicopathologic ILD occurring in cigarette smokers in whom surgical lung biopsy revealed only RB. In patients with RB-ILD, the lesion of RB is not felt to be a mere indicator of exposure to smoking but rather constitutes the primary and only histopathologic lesion accountable for the observed diffuse lung disease. Following the original description by Myers and colleagues, other reports described with greater detail the clinical and radiologic features of RB-ILD as a specific interstitial and bronchiolar process occurring in smokers and defined by the presence of RB as the only definable pathologic abnormality present on lung biopsy.[1,8,61]

The true prevalence of RB-ILD is difficult to estimate because many patients with this disorder may be asymptomatic.[4] The duration of exposure to cigarette smoke need not be lengthy or severe, although many have substantial cumulative tobacco exposures.[1] Most patients present in the fourth and fifth decade of life, and there is no gender predilection.[3,4,32] A clinicopathologic syndrome indistinguishable from RB-ILD can occasionally be encountered following exposure to solder fumes,[8] diesel smoke, and fiberglass.[1]

RB-ILD usually presents in a nonspecific manner with chronic cough and exertional dyspnea; rarely, acute presentation may occur.[62] The physical examination reveals inspiratory crackles in approximately one-half of the patients, but digital clubbing is infrequent.[3,4,32] Pulmonary function testing yields various patterns including normal, obstructive, restrictive, or mixed abnormalities.[4,32] The severity of physiologic impairment, if present, is usually mild to moderate.[4]

Chest radiography reveals bilateral, fine reticular, or reticulonodular opacities in about 60% to 70% of patients but may appear normal in some patients.[4,8,32] The main findings on chest high-resolution computed tomography (HRCT) include bronchial wall thickening, fine centrilobular nodules, and patchy areas of ground-glass attenuation.[4,8,32] The ground-glass changes are typically bilateral and affect both upper and lower lung fields (**Fig. 1**).[51,63] Coexisting emphysematous changes are frequently noted but honeycombing, traction bronchiectasis, and parenchymal fibrosis are not.

The differential diagnosis of RB-ILD includes consideration of other bronchiolar diseases, including infectious bronchiolitis, follicular bronchiolitis, and diffuse aspiration bronchiolitis, and also ILDs characterized by ground-glass opacities, particularly HP and nonspecific interstitial pneumonia (NSIP). Although surgical lung biopsy is often required for a definitive diagnosis, in clinical practice, a provisional diagnosis may be established in many patients on the basis of epidemiologic, clinical, and radiologic features and reasonable exclusion of other potential

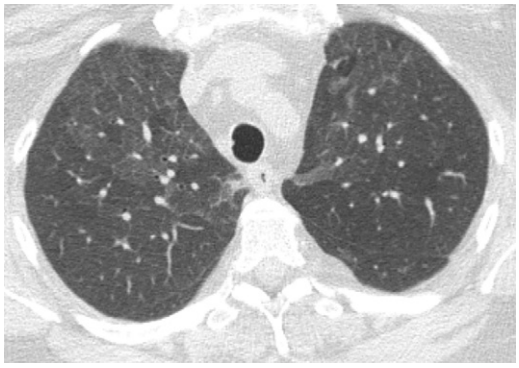

Fig. 1. RB-ILD. HRCT of the chest showing patchy areas of ground-glass attenuation in upper lung fields in a smoker with RB-ILD.

diagnoses.[8] Bronchoscopic lung biopsy has a low yield and bronchoalveolar lavage (BAL) findings are nonspecific in RB-ILD but may be diagnostically helpful in distinguishing RB-ILD from other conditions such as HP that are associated with more specific features.

The histopathologic findings required for the diagnosis of RB-ILD are those of RB and include the presence of yellow-brown–pigmented macrophages in the lumens of respiratory bronchioles, alveolar ducts, and peribronchiolar alveolar spaces without significant associated interstitial pneumonia.[4,64] At low power, these features are patchy and generally confined to peribronchiolar regions (bronchiolocentric distribution). Mild peribronchiolar fibrosis can be seen, but honeycombing is unusual.[8,63]

As in all group 1 diseases, smoking cessation is a key component of RB-ILD management. Smoking cessation may lead to improvement in radiologic abnormalities and lung function.[4,65] The degree of improvement following smoking cessation seems to be limited in some patients, and abnormalities may persist for years.[1,32] For patients with significant lung impairment, corticosteroids or other immunosuppressive medications have been used in an attempt to limit progression of lung disease; however, evidence of their effectiveness is lacking.[4,32] Most patients with RB-ILD have a relatively good prognosis, and mortality from RB-ILD is uncommon.[4,32] Although smoking cessation may lead to disease remission in some patients with RB-ILD, longitudinal studies have shown that some patients remain symptomatic for years after smoking cessation.[32]

DIP

DIP was originally believed to be a diffuse lung disease resulting from desquamation of alveolar epithelial cells into the alveolar space but later was recognized as a process of alveolar filling from macrophage accumulation.[66] DIP is associated with cigarette smoking in at least two-thirds of cases[4,7,61] but can also be seen in nonsmokers, particularly in the context of autoimmune diseases,[43] some infections,[67] and drug exposures.[67,68] It has been reported to occur in children as well as adults.[4]

The clinical presentation of DIP is nonspecific with dyspnea and cough, and physical examination reveals inspiratory crackles in approximately 60% and digital clubbing in 25% to 50% of patients.[4] Pulmonary function testing reveals restriction in one-third of cases, normal findings in 10% to 20%, and a mixed defect in the remainder.[4]

Chest radiography typically reveals patchy haziness or interstitial patterns with lower zone predominance.[4,69] The striking abnormality on HRCT is ground-glass opacities predominantly in the lower lung zones and often in a peripheral distribution (**Fig. 2**).[70] Irregular linear opacities are frequently present; however, honeycombing and significant architectural distortion are uncommon. In some instances, patients with DIP have been reported to develop HRCT findings suggestive of fibrotic NSIP (irregular linear opacities) on longitudinal follow-up.[3,71] Small parenchymal cysts and apical emphysematous changes may also be seen.[72]

On light microscopy, lung biopsies show characteristic filling of alveolar spaces with pigment-laden alveolar macrophages.[7] Although both RB-ILD and DIP are associated with the accumulation of pigment-laden macrophages in alveolar spaces, the distribution of abnormality is more bronchiolocentric and patchy in RB, whereas in DIP it tends to be more diffuse.[6] The extent of interstitial fibrosis, lymphoid follicles, and eosinophilic infiltration has been reported to be more

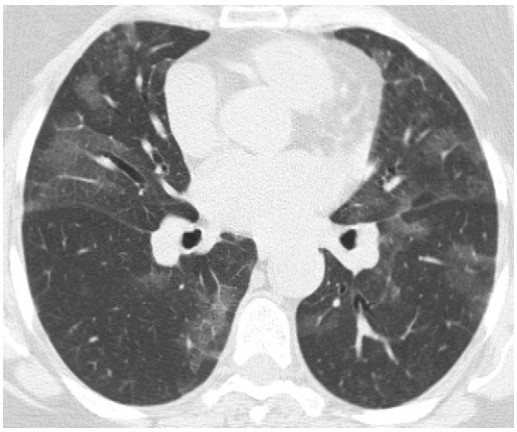

Fig. 2. DIP. HRCT of the chest showing more extensive ground-glass opacities in a smoker with DIP.

prevalent in DIP than RB-ILD.[7,61] Fibroblast foci are not seen, and the DIP lesion appears temporally uniform.[64] A definitive diagnosis of DIP usually requires surgical lung biopsy because it may be difficult to reliably differentiate DIP from NSIP or RB-ILD by clinical, radiologic, and bronchoscopic criteria.[6]

For those patients with DIP who are smokers, smoking cessation is an essential component of therapy. Prolonged remission of DIP after smoking cessation has been described, but, like all other smoking-related ILDs, the effect of smoking cessation on the natural history of DIP remains poorly characterized.[4,73] Although most patients with DIP have a relatively good prognosis with a better than 90% 5-year survival,[74] some patients progress to respiratory failure and premature death within 5 to 10 years after the diagnosis.[4,7] Patients with DIP are frequently treated with corticosteroids, but the effectiveness of steroid therapy is variable and has not been evaluated in a prospective study.[4] Other immunosuppressants such as azathioprine and methotrexate have been used in anecdotal cases.[75] Lung transplantation is an option for patients with progressive disease, but DIP can recur in the transplanted lung.[76,77]

PLCH

PLCH (also referred to as pulmonary Langerhans granulomatosis, pulmonary eosinophilic granuloma, or histiocytosis X) is induced by cigarette smoke exposure in most adult patients diagnosed to have this disorder and is characterized by accumulation of CD1a-expressing Langerhans cells in the lung and occasionally in other organ systems.[78,79] Adult PLCH forms part of the spectrum of histiocytic diseases, which ranges from relatively benign processes such as unifocal Langerhans cell histiocytosis (LCH) involving bone to disseminated multiorgan forms associated with significant morbidity and mortality.[80] Contrary to DIP and RB-ILD, which exclusively affect the lungs, approximately 15% of adult patients with PLCH may have disease outside the thoracic cavity.[5,81] PLCH represents approximately 5% of the total number of diffuse lung diseases diagnosed by lung biopsy.[81] PLCH tends to affect younger adults in their third and fourth decades.[5] PLCH seems to affect both men and women equally.

Approximately 95% of adults with PLCH are active or former smokers or have been exposed to substantial second-hand cigarette smoke.[2,49,81,82] Although the pathogenesis remains poorly understood, it is likely that cigarette smoke constituents activate epithelial cells and other cell types in the airways to produce cytokines that promote recruitment, activation, and retention of Langerhans cells in the subepithelial regions of the airways.[53,54,83] Cigarette smoke also induces the production of cytokines with profibrotic functions, such as TGF-β; in turn, TGF-β and other cytokines such as GM-CSF may further promote local expansion of Langerhans cells and facilitate the development of tissue remodeling and fibrosis as is evident in more advanced PLCH cases.[84] It is possible that certain cigarette smoke constituents are taken up by immune or other cells and result in direct immune cell activation in peribronchiolar regions. Activated Langerhans cells and macrophages in peribronchiolar regions are likely to then promote secondary recruitment of T cells, plasma cells, and eosinophils, resulting in the formation of eosinophilic granulomatous inflammation from which the descriptive term eosinophilic granuloma is derived.

As in other smoking-related ILDs, the clinical presentation tends to be nonspecific and includes dry cough and shortness of breath. About one-third of patients are asymptomatic.[5] Constitutional symptoms occur in approximately 20% to 30% of patients, whereas few patients (around 10%–15%) may present with a spontaneous pneumothorax, which can be recurrent.[5,85] Rarely, patients may present with symptoms related to extrapulmonary manifestation, such as skin, lymph node, or bony involvement.

Pulmonary function testing demonstrates variable results and may show obstructive, restrictive, mixed, or nonspecific abnormalities; pulmonary function testing may at times be completely normal.[5] Physiologic studies reveal limitations in the exercise capacity that can occur even with relatively normal resting ventilatory function. Exercise limitation correlates with markers of pulmonary vascular dysfunction, implying vascular involvement as an important cause of exercise limitation in these patients.[86]

The chest radiograph is usually abnormal and shows reticulonodular opacities more prominent in the middle and upper lung zones.[87] The HRCT of the chest often reveals characteristic abnormalities that include nodules and cysts in varying combinations bilaterally with relative sparing of the lung bases (**Fig. 3**). Nodules with or without cavitation predominate in early disease, whereas cystic changes predominate in more advanced disease.[87,88] A bronchoscopic or surgically obtained lung biopsy is recommended to confirm the diagnosis but is not always necessary. Bronchoscopy is diagnostically useful if elevated percentage of CD1a-positive cells is identified in the BAL fluid, with 5% or more being virtually diagnostic of PLCH.[89,90]

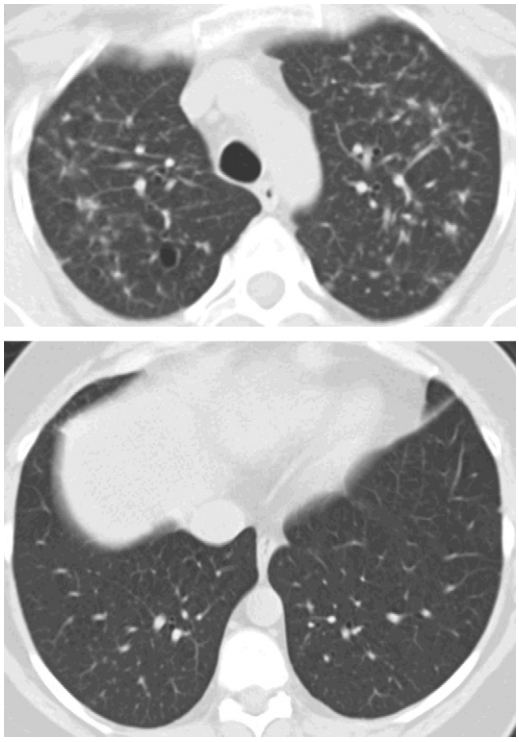

Fig. 3. PLCH. HRCT of the chest demonstrating a combination of nodular and cystic lesions in the upper lung fields and relative sparing of the lung bases in a smoker with PLCH.

Histologic features of early PLCH include loosely formed nodules of mixed inflammatory cells centered on small airways in a bronchiolocentric pattern.[48] These bronchiolocentric lesions of pulmonary LCH typically form stellate lesions with central scarring.[64] Langerhans cells are abundant in early lesions and may be identified by immunohistochemical staining for the CD1a or langerin cell surface antigens or by the identification of intracellular Birbeck granules (pentalaminar rod-shaped intracellular structures) by electron microscopy.[49,64,90,91] Eosinophilic infiltration is often encountered and may be quite extensive earlier in the course of the disease.[49,64,90,91] Varying degrees of parenchymal infiltration with macrophages, lymphocytes, and eosinophils are noted, and, in rare cases, extensive alveolar macrophage infiltration causes a pseudo-DIP reaction.[48] Some cases are associated with extensive vascular infiltration of inflammatory cells, resulting in a proliferative vasculopathy involving both arteries and veins.[92]

A critical component in the management of PLCH is smoking cessation. Smoking cessation often leads to stabilization of symptoms and radiologic abnormalities.[5,28,30,93] However, some individuals may show disease progression leading to respiratory failure despite smoking cessation.[5] There is no biomarker to predict which patient will improve and who will continue to get worse despite smoking cessation. For patients with severe disease, systemic pharmacotherapy is often considered in addition to smoking cessation. Corticosteroid therapy in the form of oral prednisone, 40 to 60 mg daily with slow tapering over months, has historically been used to treat patients with severe or progressive disease, but the data on therapeutic benefit of corticosteroids are limited.[81] Because of the perceived lack of effectiveness of corticosteroids, several other immunosuppressive agents, namely, vinblastine, chlorodeoxyadenosine (also known as 2-CDA),[94] cyclophosphamide, and methotrexate, have been used to treat progressive PLCH.[81] Chlorodeoxyadenosine has been successfully used in the management of multisystem LCH involving bone and skin, but its utility in the management of smoking-related PLCH is not well defined.[94,95] Whether immunosuppressive therapy is effective in the management of patients with progressive disease who continue to smoke is currently not known.

Management of PLCH also includes treating associated complications and sequelae, such as pneumothorax, pulmonary hypertension, and respiratory failure.[5,78,85,92] Pneumothorax is generally managed initially by chest tube drainage. Pleurodesis should be considered for most patients with spontaneous pneumothorax associated with PLCH because the recurrence rate of pneumothorax with conservative management only is approximately 60%.[85] Pulmonary hypertension is a complication that can be seen even in the absence of severe ventilatory impairment or hypoxemia in patients with PLCH and is present in nearly all patients with advanced disease.[81,92] The presence of pulmonary hypertension portends a poor prognosis.[81,92] The authors routinely perform a 2-dimensional echocardiogram in patients with PLCH at the time of diagnosis and later in the clinical course if dyspnea or the degree of hypoxemia seems out of proportion to the severity of ventilatory impairment on pulmonary function testing.[81] If the patient has echocardiographic evidence of pulmonary hypertension, a right heart catheterization should be performed to confirm the presence, determine the severity, and assess response to vasomodulator therapy. The use of vasomodulators such as the endothelin antagonist bosentan and the phosphodiesterase inhibitor sildenafil should be considered in patients with moderate to severe pulmonary hypertension.[96]

Overall, most patients with PLCH have a relatively good prognosis, particularly if complete smoking cessation is achieved. The overall median survival from time of diagnosis is approximately 13 years, with 5-year and 10-year survival rates of 75% and 64%, respectively.[81] Some individuals may progress to extensive pulmonary scarring and cystic changes leading to respiratory failure.[51,81] Lung transplantation is an option for patients with advanced PLCH. The overall survival of patients with PLCH with lung transplants is comparable to that of individuals with other indications for lung transplantation.[34,97] Recurrence of PLCH in the transplanted lung, even after smoking cessation, has been described in a few cases.[33,34,98]

ACUTE ILD ASSOCIATED WITH SMOKING

AEP is an acute respiratory illness characterized by bilateral lung opacities, hypoxemia, and pulmonary eosinophilia.[99] Although some cases of AEP are idiopathic, other cases have been linked to multiple etiologic factors including drugs,[100–103] toxin inhalation,[104] infections,[105,106] heavy metals,[104] and (more recently) cigarette smoke.[12,107,108] In 2004, 18 cases of AEP were documented among American military personnel deployed in the Iraq war.[25] The individuals affected were aged between 19 and 47 years; all were smokers, and 78% of them had begun smoking within 2 weeks to 2 months before the onset of illness.[25] Similar reports from Japan had previously described young adults with AEP occurring shortly after starting smoking.[9,10,35]

Very little is known regarding the pathogenesis of AEP. It is possible, although not proven, that acute cigarette smoke exposure coupled with other proallergic exposures may facilitate the generation of cytokines (eg, IL-5) that enable massive recruitment and activation of eosinophils in the lungs.[109,110] Eosinophilic infiltration may subsequently promote direct damage to the lung tissue by release of soluble factors in eosinophilic granules.

The presentation of AEP may be mistaken for community-acquired pneumonia or acute respiratory distress syndrome depending on the severity of the illness. After initial presentation, the illness may progress rapidly over a 7- to 14-day period to diffuse pulmonary opacities and respiratory failure. Chest radiography typically shows bilateral alveolar opacities and small pleural effusions (**Fig. 4**). Chest CT usually reveals patchy alveolar opacities of ground-glass and/or consolidative character, interlobular septal thickening, and pleural effusions.[111] Diagnosis rests on the identification of more than 20% eosinophils in the BAL fluid combined with the appropriate clinicoradiologic context.[112–114]

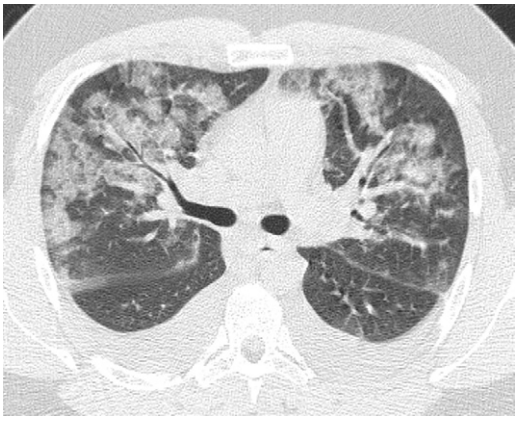

Fig. 4. AEP. HRCT of the chest revealing bilateral consolidative and ground-glass opacities as well as pleural effusions in a 22-year-old man with AEP. The patient had begun smoking cigarettes 3 weeks before this evaluation of progressive dyspnea.

The peripheral eosinophil count may be normal at presentation but is commonly elevated later in the clinical course.[112–114] Transbronchial lung biopsy is usually not required for diagnosis but when performed reveals marked eosinophilic infiltration in the interstitium and the alveoli.[115] The alveolar architecture is usually preserved.

Treatment consists of smoking cessation and corticosteroid therapy, for example, prednisone 40 to 60 mg/d, which usually results in relatively rapid improvement of respiratory insufficiency, pulmonary opacities, and pleural effusions.[25,116] The prognosis in cases that are appropriately treated is generally excellent, although few deaths have been reported caused by refractory respiratory failure.[25,116] After recovery, most patients have no long-term sequelae.[25,116]

Aside from AEP, cigarette smoking has also been implicated as an etiologic factor in acute pulmonary hemorrhage occurring in patients with Goodpasture syndrome, a pulmonary-renal syndrome associated with circulating anti–glomerular basement membrane (GBM) antibodies.[11,117] In a study of 51 patients with glomerulonephritis associated with anti-GBM antibodies, pulmonary hemorrhage occurred in all the cigarette smokers compared with only 20% of nonsmokers.[11] In addition, resumption of smoking was followed by recrudescence of pulmonary hemorrhage in 1 patient.[11]

SMOKING AND PULMONARY FIBROSIS

There are other diffuse fibrotic lung diseases that occur at a higher frequency in cigarette smokers than nonsmokers, but the cause-effect relationship is not well defined. For example, although

there are several studies that have shown UIP, the histopathologic lesion in IPF, to be more common among smokers, there are limited data that cigarette smoking directly causes interstitial fibrosis.[14,17,118] It is conceivable that cigarette smoke might act as a cofactor along with some other unknown environmental or endogenous profibrotic stimuli in susceptible individuals and promote interstitial fibrosis or possibly UIP. Smoking has also been reported to influence the clinical course associated with UIP.[119] A study on survival in patients with IPF showed that current smokers with IPF may have a survival advantage compared with those with IPF who quit smoking or never smoked. However, in multivariate analysis, this protective effect was lost, and both current and former smokers were observed to have a greater risk of death than those who never smoked.[119] The putative protective effect of smoking was also brought into question in a study of 249 patients with IPF in whom severity-adjusted survival was higher amongst those who never smoked.[118] This study demonstrated that severity-adjusted survival was higher in nonsmokers than either former smokers or the combined group of former and current smokers and showed that the presumed protective smoking effect is likely because of less severe disease at presentation in smokers or former smokers.

Some smokers manifest a combination of emphysema with fibrosis. In such patients, spirometric values may underestimate the degree of pulmonary dysfunction due to counteracting physiologic processes.[120,121] However, severe impairment of gas exchange will be evident, including a low diffusing capacity. These patients with combined pulmonary fibrosis and emphysema have a high prevalence of pulmonary hypertension and poor prognosis.[120,121]

Cigarette smokers are also at increased risk of developing RA, and individuals with established RA are at higher risk of developing ILD than nonsmokers with RA. A study of 336 patients with RA found that those with a more than 25 pack-year smoking history were significantly more likely to have radiologic evidence of ILD (odds ratio [OR], 3.76; 95% confidence interval [CI], 1.59–8.88).[15] Cigarette smoking likely represents the principal preventable risk factor for RA-associated ILD.

The significance of interstitial opacities in smokers without clinically evident ILD is not well defined. Recently, Washko and colleagues[122] analyzed data from a large cohort of smokers included in the COPDGene study and reported interstitial radiographic abnormalities in 8% of this population. The presence of radiographic interstitial abnormalities correlated with less radiographic emphysema and a greater likelihood of spirometric restrictive impairment. The most frequently observed interstitial abnormalities on HRCT were centrilobular or peribronchial ground-glass opacities and subpleural reticular, nodular, or ground-glass opacities. Although histopathologic findings were not available for this study population, centrilobular nodules and ground-glass opacities most likely represent respiratory bronchiolitis, which is ubiquitous in smokers. It is tempting to speculate that the observed peripheral subpleural radiographic abnormality in older subjects is an early subclinical form of pulmonary fibrosis similar to that seen in IPF.[123]

ILDs THAT ARE LESS COMMON IN SMOKERS

HP is an allergic immune-mediated interstitial and small airway disease that may be induced by exposure to many different types of antigens in the environment. HP has been reported to occur less frequently among smokers than nonsmokers.[124] Potential mechanisms by which cigarette smoking may decrease the risk of HP in individuals exposed to antigens include inhibition of macrophage and dendritic cell costimulatory capacity, suppression of cytokines such as IL-12 by activated dendritic cells, and suppression of T-cell function.[40,125] However, HP can and does occur in smokers.[126] In one study that compared the clinical features of HP in smokers and nonsmokers, recurrence of symptoms following diagnosis and vital capacity measurements were worse in smokers.[126]

Sarcoidosis is another ILD that is less common in smokers than nonsmokers.[19] In a large case control study on etiologic factors in sarcoidosis, a history of cigarette smoking was less frequent among the 706 subjects with sarcoidosis than control subjects (OR, 0.62; 95% CI, 0.50–0.77).[127] Although smoking reduces the prevalence of sarcoidosis, it does not confer any benefit to patients with established sarcoidosis who may have a worse outcome than nonsmokers with sarcoidosis.[23]

SUMMARY

Substantial evidence implicates cigarette smoking as the principal etiologic factor responsible for the development of RB-ILD, DIP, and PLCH. Cigarette smoking is an important precipitant of AEP and pulmonary hemorrhage in patients with Goodpasture syndrome, and smokers are at higher risk

of developing IPF and RA-associated ILD. It is important to recognize and continue to investigate the role of cigarette smoke in the pathogenesis and clinical course of these diverse diffuse lung diseases. Although relatively uncommon, these diseases are a significant health burden and frequently affect young adults in their most productive years. With the global increase in the prevalence of cigarette smoking, particularly in developing countries, it is likely that the burden of tobacco-related diseases, including smoking-related ILDs, will become heavier. Practitioners should use and recognize smoking cessation strategies as a critical component of therapy for these patients, with corticosteroids and other immune-modifying agents used as adjunctive treatments.

REFERENCES

1. Fraig M, Shreesha U, Savici D, et al. Respiratory bronchiolitis: a clinicopathologic study in current smokers, ex-smokers, and never-smokers. Am J Surg Pathol 2002;26(5):647–53.
2. Friedman PJ, Liebow AA, Sokoloff J. Eosinophilic granuloma of lung. Clinical aspects of primary histiocytosis in the adult. Medicine (Baltimore) 1981; 60(6):385–96.
3. Ryu JH, Colby TV, Hartman TE, et al. Smoking-related interstitial lung diseases: a concise review. Eur Respir J 2001;17(1):122–32.
4. Ryu JH, Myers JL, Capizzi SA, et al. Desquamative interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung disease. Chest 2005; 127(1):178–84.
5. Vassallo R, Ryu JH, Schroeder DR, et al. Clinical outcomes of pulmonary Langerhans'-cell histiocytosis in adults. N Engl J Med 2002;346(7):484–90.
6. Vassallo R, Jensen EA, Colby TV, et al. The overlap between respiratory bronchiolitis and desquamative interstitial pneumonia in pulmonary Langerhans cell histiocytosis: high-resolution CT, histologic, and functional correlations. Chest 2003;124(4): 1199–205.
7. Craig PJ, Wells AU, Doffman S, et al. Desquamative interstitial pneumonia, respiratory bronchiolitis and their relationship to smoking. Histopathology 2004;45(3):275–82.
8. Moon J, du Bois RM, Colby TV, et al. Clinical significance of respiratory bronchiolitis on open lung biopsy and its relationship to smoking related interstitial lung disease. Thorax 1999;54(11): 1009–14.
9. Nakajima M, Matsushima T. Acute eosinophilic pneumonia following cigarette smoking. Intern Med 2000;39(10):759–60.
10. Watanabe K, Fujimura M, Kasahara K, et al. Acute eosinophilic pneumonia following cigarette smoking: a case report including cigarette-smoking challenge test. Intern Med 2002;41(11):1016–20.
11. Donaghy M, Rees AJ. Cigarette smoking and lung haemorrhage in glomerulonephritis caused by autoantibodies to glomerular basement membrane. Lancet 1983;2(8364):1390–3.
12. Nakajima M, Manabe T, Niki Y, et al. A case of cigarette smoking-induced acute eosinophilic pneumonia showing tolerance. Chest 2000;118(5): 1517–8.
13. Kitahara Y, Matsumoto K, Taooka Y, et al. Cigarette smoking-induced acute eosinophilic pneumonia showing tolerance in broncho-alveolar lavage findings. Intern Med 2003;42(10):1016–21.
14. Miyake Y, Sasaki S, Yokoyama T, et al. Occupational and environmental factors and idiopathic pulmonary fibrosis in Japan. Ann Occup Hyg 2005;49(3):259–65.
15. Saag KG, Kolluri S, Koehnke RK, et al. Rheumatoid arthritis lung disease. Determinants of radiographic and physiologic abnormalities. Arthritis Rheum 1996;39(10):1711–9.
16. Wolfe F. The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis. J Rheumatol 2000;27(3):630–7.
17. Baumgartner KB, Samet JM, Stidley CA, et al. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1997;155(1): 242–8.
18. Luukkainen R, Saltyshev M, Pakkasela R, et al. Relationship of rheumatoid factor to lung diffusion capacity in smoking and non-smoking patients with rheumatoid arthritis. Scand J Rheumatol 1995;24(2):119–20.
19. Valeyre D, Soler P, Clerici C, et al. Smoking and pulmonary sarcoidosis: effect of cigarette smoking on prevalence, clinical manifestations, alveolitis, and evolution of the disease. Thorax 1988;43(7): 516–24.
20. Hance AJ, Basset F, Saumon G, et al. Smoking and interstitial lung disease. The effect of cigarette smoking on the incidence of pulmonary histiocytosis X and sarcoidosis. Ann N Y Acad Sci 1986;465: 643–56.
21. Warren CP. Extrinsic allergic alveolitis: a disease commoner in non-smokers. Thorax 1977;32(5): 567–9.
22. Douglas JG, Middleton WG, Gaddie J, et al. Sarcoidosis: a disorder commoner in non-smokers? Thorax 1986;41(10):787–91.
23. Peros-Golubicic T, Ljubic S. Cigarette smoking and sarcoidosis. Acta Med Croatica 1995;49(4–5): 187–93.
24. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking

may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54(1):38–46.
25. Shorr AF, Scoville SL, Cersovsky SB, et al. Acute eosinophilic pneumonia among US Military personnel deployed in or near Iraq. JAMA 2004; 292(24):2997–3005.
26. Girard M, Israel-Assayag E, Cormier Y. Pathogenesis of hypersensitivity pneumonitis. Curr Opin Allergy Clin Immunol 2004;4(2):93–8.
27. Patel RR, Ryu JH, Vassallo R. Cigarette smoking and diffuse lung disease. Drugs 2008;68(11): 1511–27.
28. Mogulkoc N, Veral A, Bishop PW, et al. Pulmonary Langerhans' cell histiocytosis: radiologic resolution following smoking cessation. Chest 1999;115(5): 1452–5.
29. Zeid NA, Muller HK. Tobacco smoke induced lung granulomas and tumors: association with pulmonary Langerhans cells. Pathology 1995; 27(3):247–54.
30. Negrin-Dastis S, Butenda D, Dorzee J, et al. Complete disappearance of lung abnormalities on high-resolution computed tomography: a case of histiocytosis X. Can Respir J 2007;14(4):235–7.
31. Bernstrand C, Cederlund K, Ashtrom L, et al. Smoking preceded pulmonary involvement in adults with Langerhans cell histiocytosis diagnosed in childhood. Acta Paediatr 2000;89(11): 1389–92.
32. Portnoy J, Veraldi KL, Schwarz MI, et al. Respiratory bronchiolitis-interstitial lung disease: long-term outcome. Chest 2007;131(3):664–71.
33. Etienne B, Bertocchi M, Gamondes JP, et al. Relapsing pulmonary Langerhans cell histiocytosis after lung transplantation. Am J Respir Crit Care Med 1998;157(1):288–91.
34. Dauriat G, Mal H, Thabut G, et al. Lung transplantation for pulmonary Langerhans' cell histiocytosis: a multicenter analysis. Transplantation 2006;81(5): 746–50.
35. Shiota Y, Kawai T, Matsumoto H, et al. Acute eosinophilic pneumonia following cigarette smoking. Intern Med 2000;39(10):830–3.
36. Alp H, Daum RS, Abrahams C, et al. Acute eosinophilic pneumonia: a cause of reversible, severe, noninfectious respiratory failure. J Pediatr 1998; 132(3 Pt 1):540–3.
37. Nakagome K, Kato J, Kubota S, et al. [Acute eosinophilic pneumonia induced by cigarette smoking]. Nihon Kokyuki Gakkai Zasshi 2000;38(2):113–6 [in Japanese].
38. Katzenstein AL, Mukhopadhyay S, Zanardi C, et al. Clinically occult interstitial fibrosis in smokers: classification and significance of a surprisingly common finding in lobectomy specimens. Hum Pathol 2010;41(3):316–25.
39. Vassallo R, Tamada K, Lau JS, et al. Cigarette smoke extract suppresses human dendritic cell function leading to preferential induction of Th-2 priming. J Immunol 2005;175(4):2684–91.
40. Israel-Assayag E, Dakhama A, Lavigne S, et al. Expression of costimulatory molecules on alveolar macrophages in hypersensitivity pneumonitis. Am J Respir Crit Care Med 1999;159(6):1830–4.
41. Anderson K, Morrison SM, Bourke S, et al. Effect of cigarette smoking on the specific antibody response in pigeon fanciers. Thorax 1988;43(10):798–800.
42. Cormier Y, Belanger J, Durand P. Factors influencing the development of serum precipitins to farmer's lung antigen in Quebec dairy farmers. Thorax 1985;40(2):138–42.
43. Hakala M, Paakko P, Huhti E, et al. Open lung biopsy of patients with rheumatoid arthritis. Clin Rheumatol 1990;9(4):452–60.
44. Churg A, Muller NL, Flint J, et al. Chronic hypersensitivity pneumonitis. Am J Surg Pathol 2006;30(2): 201–8.
45. Ranney L, Melvin C, Lux L, et al. Systematic review: smoking cessation intervention strategies for adults and adults in special populations. Ann Intern Med 2006;145(11):845–56.
46. Kuschner WG, D'Alessandro A, Wong H, et al. Dose-dependent cigarette smoking-related inflammatory responses in healthy adults. Eur Respir J 1996;9(10):1989–94.
47. Casolaro MA, Bernaudin JF, Saltini C, et al. Accumulation of Langerhans' cells on the epithelial surface of the lower respiratory tract in normal subjects in association with cigarette smoking. Am Rev Respir Dis 1988;137(2):406–11.
48. Colby TV, Lombard C. Histiocytosis X in the lung. Hum Pathol 1983;14(10):847–56.
49. Travis WD, Borok Z, Roum JH, et al. Pulmonary Langerhans cell granulomatosis (histiocytosis X). A clinicopathologic study of 48 cases. Am J Surg Pathol 1993;17(10):971–86.
50. Myers JL, Veal CF Jr, Shin MS, et al. Respiratory bronchiolitis causing interstitial lung disease. A clinicopathologic study of six cases. Am Rev Respir Dis 1987;135(4):880–4.
51. Remy-Jardin M, Remy J, Gosselin B, et al. Lung parenchymal changes secondary to cigarette smoking: pathologic-CT correlations. Radiology 1993;186(3):643–51.
52. Tomita K, Caramori G, Lim S, et al. Increased p21(CIP1/WAF1) and B cell lymphoma leukemia-x(L) expression and reduced apoptosis in alveolar macrophages from smokers. Am J Respir Crit Care Med 2002;166(5):724–31.
53. Tazi A, Bonay M, Bergeron A, et al. Role of granulocyte-macrophage colony stimulating factor (GM-CSF) in the pathogenesis of adult pulmonary histiocytosis X. Thorax 1996;51(6):611–4.

54. Tazi A, Bouchonnet F, Grandsaigne M, et al. Evidence that granulocyte macrophage-colony-stimulating factor regulates the distribution and differentiated state of dendritic cells/Langerhans cells in human lung and lung cancers. J Clin Invest 1993;91(2):566–76.
55. Wang RD, Wright JL, Churg A. Transforming growth factor-beta1 drives airway remodeling in cigarette smoke-exposed tracheal explants. Am J Respir Cell Mol Biol 2005;33(4):387–93.
56. D'Hulst AI, Vermaelen KY, Brusselle GG, et al. Time course of cigarette smoke-induced pulmonary inflammation in mice. Eur Respir J 2005;26(2): 204–13.
57. Lu LM, Zavitz CC, Chen B, et al. Cigarette smoke impairs NK cell-dependent tumor immune surveillance. J Immunol 2007;178(2):936–43.
58. Kode A, Yang SR, Rahman I. Differential effects of cigarette smoke on oxidative stress and proinflammatory cytokine release in primary human airway epithelial cells and in a variety of transformed alveolar epithelial cells. Respir Res 2006;7:132.
59. Yang SR, Chida AS, Bauter MR, et al. Cigarette smoke induces proinflammatory cytokine release by activation of NF-kappaB and posttranslational modifications of histone deacetylase in macrophages. Am J Physiol Lung Cell Mol Physiol 2006;291(1):L46–57.
60. Niewoehner DE, Kleinerman J, Rice DB. Pathologic changes in the peripheral airways of young cigarette smokers. N Engl J Med 1974;291(15): 755–8.
61. Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin Proc 1989;64(11):1373–80.
62. Mavridou D, Laws D. Respiratory bronchiolitis associated interstitial lung disease (RB-ILD): a case of an acute presentation. Thorax 2004; 59(10):910–1.
63. Hartman TE, Tazelaar HD, Swensen SJ, et al. Cigarette smoking: CT and pathologic findings of associated pulmonary diseases. Radiographics 1997; 17(2):377–90.
64. Aubry MC, Wright JL, Myers JL. The pathology of smoking-related lung diseases. Clin Chest Med 2000;21(1):11–35, vii.
65. Wells AU, Nicholson AG, Hansell DM, et al. Respiratory bronchiolitis-associated interstitial lung disease. Semin Respir Crit Care Med 2003; 24(5):585–94.
66. Liebow AA, Steer A, Billingsley JG. Desquamative interstitial pneumonia. Am J Med 1965;39:369–404.
67. Iskandar SB, McKinney LA, Shah L, et al. Desquamative interstitial pneumonia and hepatitis C virus infection: a rare association. South Med J 2004; 97(9):890–3.
68. Flores-Franco RA, Luevano-Flores E, Gaston-Ramirez C. Sirolimus-associated desquamative interstitial pneumonia. Respiration 2007;74(2): 237–8.
69. Hansell DM, Nicholson AG. Smoking-related diffuse parenchymal lung disease: HRCT-pathologic correlation. Semin Respir Crit Care Med 2003;24(4):377–92.
70. Heyneman LE, Ward S, Lynch DA, et al. Respiratory bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease, and desquamative interstitial pneumonia: different entities or part of the spectrum of the same disease process? AJR Am J Roentgenol 1999;173(6):1617–22.
71. Hartman TE, Primack SL, Kang EY, et al. Disease progression in usual interstitial pneumonia compared with desquamative interstitial pneumonia. Assessment with serial CT [see comment]. Chest 1996;110(2):378–82.
72. Mueller-Mang C, Grosse C, Schmid K, et al. What every radiologist should know about idiopathic interstitial pneumonias. Radiographics 2007;27(3): 595–615.
73. Matsuo K, Tada S, Kataoka M, et al. Spontaneous remission of desquamative interstitial pneumonia. Intern Med 1997;36(10):728–31.
74. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;157(1):199–203.
75. Flusser G, Gurman G, Zirkin H, et al. Desquamative interstitial pneumonitis causing acute respiratory failure, responsive only to immunosuppressants. Respiration 1991;58(5–6):324–6.
76. Timmer SJ, Karamzadeh AM, Yung GL, et al. Predicting survival of lung transplantation candidates with idiopathic interstitial pneumonia: does PaO(2) predict survival? Chest 2002; 122(3):779–84.
77. Verleden GM, Sels F, Van Raemdonck D, et al. Possible recurrence of desquamative interstitial pneumonitis in a single lung transplant recipient. Eur Respir J 1998;11(4):971–4.
78. Vassallo R, Ryu JH, Colby TV, et al. Pulmonary Langerhans'-cell histiocytosis. N Engl J Med 2000;342(26):1969–78.
79. Tazi A. Adult pulmonary Langerhans' cell histiocytosis. Eur Respir J 2006;27(6):1272–85.
80. Favara BE, Feller AC, Pauli M, et al. Contemporary classification of histiocytic disorders. The WHO Committee On Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. Med Pediatr Oncol 1997;29(3): 157–66.
81. Chaowalit N, Pellikka PA, Decker PA, et al. Echocardiographic and clinical characteristics of pulmonary hypertension complicating pulmonary

Langerhans cell histiocytosis. Mayo Clin Proc 2004;79(10):1269–75.
82. Delobbe A, Durieu J, Duhamel A, et al. Determinants of survival in pulmonary Langerhans' cell granulomatosis (histiocytosis X). Groupe d'Etude en Pathologie Interstitielle de la Societe de Pathologie Thoracique du Nord. Eur Respir J 1996;9(10): 2002–6.
83. Aguayo SM, King TE Jr, Waldron JA Jr, et al. Increased pulmonary neuroendocrine cells with bombesin-like immunoreactivity in adult patients with eosinophilic granuloma. J Clin Invest 1990;86(3):838–44.
84. Asakura S, Colby TV, Limper AH. Tissue localization of transforming growth factor-beta1 in pulmonary eosinophilic granuloma. Am J Respir Crit Care Med 1996;154(5):1525–30.
85. Mendez JL, Nadrous HF, Vassallo R, et al. Pneumothorax in pulmonary Langerhans cell histiocytosis. Chest 2004;125(3):1028–32.
86. Crausman RS, Jennings CA, Tuder RM, et al. Pulmonary histiocytosis X: pulmonary function and exercise pathophysiology. Am J Respir Crit Care Med 1996;153(1):426–35.
87. Moore AD, Godwin JD, Muller NL, et al. Pulmonary histiocytosis X: comparison of radiographic and CT findings. Radiology 1989;172(1):249–54.
88. Brauner MW, Grenier P, Mouelhi MM, et al. Pulmonary histiocytosis X: evaluation with high-resolution CT. Radiology 1989;172(1):255–8.
89. Soler P, Chollet S, Jacque C, et al. Immunocytochemical characterization of pulmonary histiocytosis X cells in lung biopsies. Am J Pathol 1985; 118(3):439–51.
90. Chollet S, Soler P, Bernaudin JF, et al. [Exploratory bronchoalveolar lavage]. Presse Med 1984;13(24): 1503–8 [in French].
91. Yousem SA, Colby TV, Chen YY, et al. Pulmonary Langerhans' cell histiocytosis: molecular analysis of clonality. Am J Surg Pathol 2001;25(5): 630–6.
92. Fartoukh M, Humbert M, Capron F, et al. Severe pulmonary hypertension in histiocytosis X. Am J Respir Crit Care Med 2000;161(1):216–23.
93. Abbott GF, Rosado-de-Christenson ML, Franks TJ, et al. From the archives of the AFIP: pulmonary Langerhans cell histiocytosis. Radiographics 2004; 24(3):821–41.
94. Aerni MR, Aubry MC, Myers JL, et al. Complete remission of nodular pulmonary Langerhans cell histiocytosis lesions induced by 2-chlorodeoxyadenosine in a non-smoker. Respir Med 2008; 102(2):316–9.
95. Pardanani A, Phyliky RL, Li CY, et al. 2-Chlorodeoxyadenosine therapy for disseminated Langerhans cell histiocytosis. Mayo Clin Proc 2003;78(3):301–6.
96. Kiakouama L, Cottin V, Etienne-Mastroianni B, et al. Severe pulmonary hypertension in histiocytosis X: long-term improvement with bosentan. Eur Respir J 2010;36(1):202–4.
97. Saleem I, Moss J, Egan JJ. Lung transplantation for rare pulmonary diseases. Sarcoidosis Vasc Diffuse Lung Dis 2005;22(Suppl 1):S85–90.
98. Gabbay E, Dark JH, Ashcroft T, et al. Recurrence of Langerhans' cell granulomatosis following lung transplantation. Thorax 1998;53(4):326–7.
99. Philit F, Etienne-Mastroianni B, Parrot A, et al. Idiopathic acute eosinophilic pneumonia: a study of 22 patients. Am J Respir Crit Care Med 2002;166(9): 1235–9.
100. Yokoyama A, Mizushima Y, Suzuki H, et al. Acute eosinophilic pneumonia induced by minocycline: prominent Kerley B lines as a feature of positive re-challenge test. Jpn J Med 1990;29(2): 195–8.
101. Barnes MT, Bascunana J, Garcia B, et al. Acute eosinophilic pneumonia associated with antidepressant agents. Pharm World Sci 1999;21(5): 241–2.
102. Noh H, Lee YK, Kan SW, et al. Acute eosinophilic pneumonia associated with amitriptyline in a hemodialysis patient. Yonsei Med J 2001;42(3):357–9.
103. McCormick M, Nelson T. Cocaine-induced fatal acute eosinophilic pneumonia: a case report. WMJ 2007;106(2):92–5.
104. Kawayama T, Fujiki R, Morimitsu Y, et al. Fatal idiopathic acute eosinophilic pneumonia with acute lung injury. Respirology 2002;7(4):373–5.
105. Takizawa H. Acute eosinophilic pneumonia: possible role of hyperreactivity of airway epithelial cells. Intern Med 2002;41(11):917.
106. Glazer CS, Cohen LB, Schwarz MI. Acute eosinophilic pneumonia in AIDS. Chest 2001;120(5): 1732–5.
107. Miki K, Miki M, Okano Y, et al. Cigarette smoke-induced acute eosinophilic pneumonia accompanied with neutrophilia in the blood. Intern Med 2002;41(11):993–6.
108. Al-Saieg N, Moammar O, Kartan R. Flavored cigar smoking induces acute eosinophilic pneumonia. Chest 2007;131(4):1234–7.
109. Rom WN, Weiden M, Garcia R, et al. Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. Am J Respir Crit Care Med 2002;166(6):797–800.
110. Nakahara Y, Hayashi S, Fukuno Y, et al. Increased interleukin-5 levels in bronchoalveolar lavage fluid is a major factor for eosinophil accumulation in acute eosinophilic pneumonia. Respiration 2001; 68(4):389–95.
111. Daimon T, Johkoh T, Sumikawa H, et al. Acute eosinophilic pneumonia: thin-section CT findings in 29 patients. Eur J Radiol 2008;65(3):462–7.
112. Allen J. Acute eosinophilic pneumonia. Semin Respir Crit Care Med 2006;27(2):142–7.

113. King MA, Pope-Harman AL, Allen JN, et al. Acute eosinophilic pneumonia: radiologic and clinical features. Radiology 1997;203(3):715–9.
114. Allen JN, Pacht ER, Gadek JE, et al. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. N Engl J Med 1989; 321(9):569–74.
115. Tazelaar HD, Linz LJ, Colby TV, et al. Acute eosinophilic pneumonia: histopathologic findings in nine patients. Am J Respir Crit Care Med 1997;155(1): 296–302.
116. Uchiyama H, Suda T, Nakamura Y, et al. Alterations in smoking habits are associated with acute eosinophilic pneumonia. Chest 2008;133(5):1174–80.
117. Benz K, Amann K, Dittrich K, et al. Patient with antibody-negative relapse of Goodpasture syndrome. Clin Nephrol 2007;67(4):240–4.
118. Antoniou KM, Hansell DM, Rubens MB, et al. Idiopathic pulmonary fibrosis: outcome in relation to smoking status. Am J Respir Crit Care Med 2008; 177(2):190–4.
119. King TE Jr, Tooze JA, Schwarz MI, et al. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med 2001;164(7):1171–81.
120. Cottin V, Le Pavec J, Prevot G, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. Eur Respir J 2010;35(1):105–11.
121. Mejia M, Carrillo G, Rojas-Serrano J, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest 2009;136(1):10–5.
122. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med 2011; 364(10):897–906.
123. King TE Jr. Smoking and subclinical interstitial lung disease. N Engl J Med 2011;364(10):968–70.
124. Selman M. Hypersensitivity pneumonitis: a multifaceted deceiving disorder. Clin Chest Med 2004; 25(3):531–47, vi.
125. Arima K, Ando M, Ito K, et al. Effect of cigarette smoking on prevalence of summer-type hypersensitivity pneumonitis caused by Trichosporon cutaneum. Arch Environ Health 1992;47(4):274–8.
126. Ohtsuka Y, Munakata M, Tanimura K, et al. Smoking promotes insidious and chronic farmer's lung disease, and deteriorates the clinical outcome. Intern Med 1995;34(10):966–71.
127. Newman LS, Rose CS, Bresnitz EA, et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. Am J Respir Crit Care Med 2004;170(12):1324–30.