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Cigarette Smoking and Diffuse Lung Disease

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Abstract

Cigarette smoke, a toxic collection of more than 4000 chemicals generated from combustion of tobacco plant leaves, is known to cause several respiratory ailments, including chronic bronchitis, emphysema and lung cancer, and is associated with an increase in respiratory infections. In addition, cigarette smoking is considered a principal aetiological factor responsible for the development of certain diffuse interstitial and bronchiolar lung diseases, namely respiratory bronchiolitis-interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP) and adult pulmonary Langerhans' cell histiocytosis (PLCH). Although not exclusively seen in cigarette smokers, substantial clinical and epidemiological data support a central role for smoking as the primary causative agent of most RB-ILD, DIP and PLCH. Additional evidence in support of cigarette smoke as a primary aetiological agent in RB-ILD, DIP and PLCH is the observation that smoking cessation may lead to disease improvement, while recurrence of these disorders has been observed to occur in the transplanted lung upon re-exposure to tobacco smoke. Furthermore, histopathological changes of respiratory bronchiolitis, DIP and PLCH (with or without co-existent emphysema) may be found on lung biopsy in the same individual, implicating smoking as a common inciting agent of these diverse lesions. Recent studies also suggest a role for cigarette smoking as a potential co-factor in the development of acute eosinophilic pneumonia, usual interstitial pneumonia and rheumatoid arthritis-associated interstitial lung disease. In the current review, we propose a novel classification that takes into account the complex relationship between cigarette smoking and diffuse lung diseases. Investigation on the role of smoking as a potential causative factor or modifier of these diverse diffuse lung diseases is

important, as smoking cessation utilizing state-of-the-art tobacco cessation efforts should be a central part of therapy, while pharmacotherapy with corticosteroids or other immune modifying agents should be reserved for selected patients.

Cigarette smoke is a complex mixture of more than 4000 chemicals, many of which have been demonstrated to exert a variety of toxic effects on cellular function. Cigarette smoking is a complex chronic illness in which tobacco addiction, induced by chronic nicotine exposure, results in persistent exposure of the lungs and other organ systems to toxic agents present in cigarette smoke. Chronic obstructive pulmonary disease and lung cancer are the two widely known consequences of cigarette smoking. Less well appreciated are a number of non-neoplastic interstitial and bronchiolar pulmonary diseases that occur in a small proportion of cigarette smokers. These include respiratory bronchiolitis-interstitial lung disease (RB-ILD), desquamative interstitial pneumonitis (DIP) and adult pulmonary Langerhans' cell histiocytosis (PLCH).[1-7] Collectively, these diseases are often referred to as 'smoking-related interstitial lung diseases', a term coined in recognition of the likely causal association with cigarette smoking. This term has also generated some confusion because not all cases of RB-ILD, DIP or PLCH occur in active cigarette smokers.[3,5,6] In this review, the relationship between smoking and specific diffuse lung diseases is discussed, and a novel classification of the effect of cigarette smoking on diffuse lung disease is proposed. Another purpose of this review is to succinctly describe relevant features of the primary cigarette smoke-induced diffuse lung diseases, and provide an update on current pharmacological and non-pharmacological therapy of these conditions.

1. Cigarette Smoking and Diffuse Lung Disease

Although cigarette smoking seems to be the primary cause of specific diffuse lung diseases (namely RB-ILD, DIP and PLCH[1-3,5,6]), smoking also influences the clinical course of idiopathic pulmonary fibrosis,[8,9] may precipitate acute diffuse lung diseases in certain individuals (for instance, acute eosinophilic pneumonia)[10-13] and, paradoxically, may confer protection from development of other diffuse lung diseases such as hypersensitivity pneumonitis.[14] In recognition of the complex relationship between smoking and diffuse lung diseases, we propose a novel approach to classification of smoking and diffuse lung diseases, with the primary goal of subdividing diseases according to the strength of available evidence implicating smoking as an aetiological factor. Group 1 smoking-related diffuse lung diseases (table I) are strongly linked to tobacco exposure, and occur primarily (although not exclusively) in cigarette smokers.[2-6,15,16] Group 2 diseases are acute diffuse lung diseases that may be precipitated by smoking, although in many cases an association with cigarette smoking is not present.[10-13,17-20] Group 3 diseases are not directly in-

Table I. Proposed classification of smoking-related interstitial lung disease

Group	Diseases	References
1. Chronic diffuse lung diseases that are *very likely* to be caused by cigarette smoking	Respiratory bronchiolitis-interstitial lung disease Desquamative interstitial pneumonia Adult pulmonary Langerhans' cell histiocytosis	1-6,15,16,25-28
2. Diffuse lung diseases that *may be acutely precipitated* by cigarette smoking	Acute eosinophilic pneumonia Pulmonary haemorrhage syndromes	10-12,20,29
3. Interstitial lung diseases that are *statistically more prevalent* in smokers	Idiopathic pulmonary fibrosis Rheumatoid arthritis-associated interstitial lung disease	8,9,21,22,30
4. Interstitial lung diseases that are *less prevalent* in smokers	Sarcoidosis Hypersensitivity pneumonitis	23,31-34

Table II. Key characteristics of group 1 chronic smoking-related diffuse lung diseases

Characteristic	RB-ILD	DIP	PLCH
Association with cigarette smoking	95%	60–90%	95–97%
Clinical features	Chronic cough with inspiratory crackles	Chronic cough, bilateral crackles Clubbing in one-third of pts	Dyspnoea and cough Pneumothorax in 15% of pts
High resolution CT scan	Centrilobular nodules and ground-glass opacities	Ground-glass and reticular opacities	Peribronchiolar nodules and cysts
Key histological findings	Pigmented macrophages in the respiratory bronchioles and alveolar ducts	Alveolar spaces filled with pigmented macrophages	Bronchiolocentric nodules Stellate lesions CD1a-positive Langerhans' cells
Response to corticosteroids	Unknown	Modest	Modest

DIP = desquamative interstitial pneumonia; **PLCH** = pulmonary Langerhans' cell histiocytosis; **pts** = patients; **RB-ILD** = respiratory bronchiolitis-interstitial lung disease.

duced by cigarette smoking, but appear statistically more prevalent in cigarette smokers, suggesting that smoking is a potential co-factor in the pathogenesis.[9,21,22] Finally, we propose a fourth group of diffuse lung diseases (group 4, see table I), including hypersensitivity pneumonitis and sarcoidosis, which appear to be less prevalent in cigarette smokers.[23,24] In addition to being a useful academic exercise, the proposed classification (table I) also serves the purpose of illustrating the complex relationship between smoking and diffuse lung diseases, and may help in clarifying some misconceptions regarding the role of smoking in non-neoplastic lung diseases.

The group 1 diseases (table I and table II) include RB-ILD, DIP and PLCH. These three conditions are perhaps the prototypic or 'true' smoking-related diffuse lung diseases. For diseases in this group, several lines of clinical, epidemiological and laboratory evidence support a direct role for cigarette smoking in disease onset, progression and recurrence.[3,4,6,7,15,16,25,26,35,36] Multiple case series have reported a history of tobacco use in 90% or more of these patients, with the prevalence of tobacco use being highest in RB-ILD patients,[3-5,37] followed by PLCH[2,6,27] and least prevalent in DIP.[5,28] A compelling observation that favours smoking as the common precipitant of all these lesions is the reported co-occurrence of all three lesions in the same patient.[15] Indeed, it is impossible to assign a specific diagnosis of DIP, RB-ILD or PLCH in certain patients because histopathological features of all three may be seen on lung biopsy, prompting the descriptive term 'smoking-related interstitial lung disease' to encompass the presence of these aetiologically related lesions.[15] The potential for disease remission with smoking cessation (at least in some cases of PLCH and RB-ILD),[5,6,36,38] the recurrence of disease in transplanted lungs (reported with PLCH),[35,39] the occurrence of PLCH in new-onset smokers who had extra-pulmonary Langerhans' cell histiocytosis (LCH) in childhood[40] and the description of analogous lesions in mice exposed to high doses of cigarette smoke[41] all lend further support to the contention that smoking is a the primary aetiological factor in the pathogenesis of RB-ILD, DIP and PLCH.

Diseases allocated to group 2 (table I) differ because the association with cigarette smoking is less robust than 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 patients with group 2 diseases. The most relevant conditions in this category include acute eosinophilic pneumonia (AEP) and certain pulmonary haemorrhage syndromes.[10,11,13,17,20] AEP deserves particular attention because a number of recent studies have implicated recent-onset exposure to cigarette smoke as a principal inducer of this disease in some patients.[11,17,29,42,43] Of interest is the reported response of certain individuals with resolved AEP to a rechallenge with cigarette smoke exposure, which triggers peripheral eosinophilia and other pathophysiological abnormalities, suggesting that exposure to ciga-

rette smoke may induce certain responses relevant to the development of acute diffuse lung disease in susceptible hosts.[11]

Diseases included in group 3 (table I) are chronic diffuse lung diseases that are statistically more likely to develop in cigarette smokers.[9,22] For instance, cigarette smoking is known to increase the relative risk of rheumatoid arthritis-associated interstitial lung disease, possibly by triggering rheumatoid arthritis-specific immune reactions to citrullinated proteins.[22,30,44] Similarly, the relative risk of idiopathic pulmonary fibrosis developing in a smoker is higher than for a non-smoker.[9] 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. It is not appropriate to consider smoking as an inducer of these diseases, but rather a disease modifier or potentially a co-factor that facilitates the development of pro-fibrotic responses that lead to these diffuse fibrotic lung diseases.

The fourth and final group consists of diseases that are less prevalent in smokers than in non-smokers and includes sarcoidosis and hypersensitivity pneumonitis.[31-34] Cigarette smoking seems to provide certain 'protective' effects that diminish the potential development of these granulomatous inflammatory lung diseases, potentially by inhibiting certain immunological responses in the lung required for granuloma formation or the development of T helper (T_h)-1 polarized immune responses following exposure to inhaled antigens.[24,45] Epidemiological studies demonstrate that antibodies to pigeon antigens are more frequent among former or never smokers than active smokers.[14] A similar study in farmers showed that never smokers and previous smokers had a higher prevalence of serum precipitin levels to various farmers' lung antigens compared with current smokers.[46] Lung macrophages from cigarette smokers also have lower levels of co-stimulatory molecules than controls.[24] Since co-stimulatory 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.[45] It is conceivable that the diminished capacity of the macrophages and dendritic cells of smokers 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 hypersensitivity pneumonitis should not be construed as an indication to promote smoking in patients with these diseases. On the contrary, 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 RB-ILD or DIP in some patients may be induced by factors other than cigarette smoke exposure, and that some patients with classic PLCH are non-smokers, had been interpreted as implying that these disease do not necessarily represent specific smoking-induced lung pathologies. However, it is well recognized that a number of specific histopathological entities can be induced by various aetiologies, potentially a reflection that the lung has a limited number of ways in responding to various insults. For example, the lesion of usual interstitial pneumonia (UIP) may be induced by asbestos exposure, occur in patients with chronic hypersensitivity pneumonitis and occur in the context of autoimmune diseases such as rheumatoid disease.[47,48] Cigarette smoking is the most well defined aetiological factor associated with the development of RB-ILD, DIP and PLCH; however, the histopathological lesions of respiratory bronchiolitis, DIP and PLCH do not exclusively occur in smokers, and may occasionally be idiopathic or may be seen in the context of other exposures or aetiologies.[3,6,28]

Defining the relationship between smoking and specific diffuse lung diseases has important practi-

cal therapeutic implications. Smoking cessation is imperative for all the diseases listed in groups 1–3 (table I). It is our practice to employ state-of-the-art tobacco cessation strategies in these patients, and have a low threshold for referral to nicotine dependence counsellors. 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 cigarette smoke exposure. Similarly, all current smokers with diseases in groups 2 and 3 should be counselled 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 counselling and behaviour therapy, nicotine replacement therapy, and pharmacotherapy, which includes the use of bupropion, varenicline and clonidine in selected patients.[49] Unfortunately, even with state-of-the-art approaches, sustained smoking cessation rates in both outpatient and intensive inpatient practices peak at around 30%.[50] Nicotine replacement therapies in the form of nicotine gum, nasal spray or transdermal patch each have equal smoking cessation rates of approximately 13–20% at the end of 1 year depending on the study population.[51,52] This can be increased to 27% when combined with intensive counselling.[51,52] Bupropion therapy was associated with a quit rate of about 30% in one study, but the rate increased to 37% when combined with counselling.[53] The new drug varenicline induced a 44% quit rate at the end of the fourth week after 12 weeks of treatment, and continuous abstinence at the end of 1 year with varenicline was approximately 23%, compared with 16% for bupropion and 9% for placebo.[54]

2. Common Pathogenetic Mechanisms

Precise mechanisms by which smoking induces diffuse lung disease remain elusive. In subjects without clinical lung disease, cigarette smoking induces a number of inflammatory changes in the lungs, including inflammatory cell recruitment consisting primarily of macrophages, neutrophils and Langerhans' cells (a subtype of the myeloid dendritic cell family expressing surface CD1a receptors).[55,56] A perplexing and, as yet, unresolved question relates to the observation that only a very small proportion of smokers develop clinically significant diffuse lung disease, despite evidence of lung inflammation being prevalent in smokers even without overt disease. This implies a role for endogenous host factors or additional exogenous factors (a second hit) in the development of smoking-induced diffuse lung disease.[4,5]

All of the group 1 smoking-related diffuse lung diseases have prominent peribronchial inflammatory involvement,[4,15,16,25] suggesting injury of small airways by some inhaled constituents of cigarette smoke. Indeed, the primary lesion in both RB-ILD and PLCH is a bronchiolitis rather than an interstitial pulmonary process.[4,25] In addition to prominent bronchiolar inflammation, all of the group 1 diseases demonstrate an increase in macrophage numbers in the interstitium and the alveolar spaces.[16,25,57] Macrophage recruitment and accumulation in airways, interstitium and distal air spaces is a key feature of many smoking-induced lung diseases. The mechanisms by which exaggerated macrophage accumulation occurs in DIP and RB-ILD are unknown, but may involve exaggerated production of macrophage recruiting factors by alveolar and airway epithelial cells, enhanced macrophage survival, or diminished apoptosis of recruited macrophages.[58] Macrophages also form a key constituent in the cellular inflammatory infiltrate found in the lungs of patients with PLCH.[25] In these patients, lung epithelial cells have been demonstrated to aberrantly produce excessive granulocyte-macrophage colony stimulating factor, a cytokine that provides proliferative and activation signals to both macrophages and dendritic cells.[59,60] Cigarette smoke extracts have also been demonstrated to induce transforming growth factor (TGF)-β production by lung epithelial cells, a cytokine that is involved in Langerhans' cell development, immune modulation and fibrogenic responses in the airways.[61]

Cigarette smoking induces several abnormalities in immune system cells and other cells in the lungs that are probably relevant to the pathogenesis of smoking-related diffuse lung diseases.[45,62,63] 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.[64,65] It is reasonable to speculate that smokers in whom diffuse lung disease 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 anti-inflammatory mechanisms or additional exogenous insults, such as viral infections, have a role in promoting smoking-related diffuse lung diseases is unknown, but should be an important area of future research.

3. Respiratory Bronchiolitis-Interstitial Lung Disease

Niewoehner and colleagues[66] described respiratory bronchiolitis as a histopathological finding present in the majority of cigarette smokers. The principal finding in that original study was the presence of peribronchiolar pigmented macrophage accumulation, a finding reproduced in a number of subsequent case series describing lung biopsy findings of cigarette smokers.[1,3,15] Since it is a histological abnormality observed in virtually all smokers, respiratory bronchiolitis can be considered as a histological marker of smoking. The term 'respiratory bronchiolitis-interstitial lung disease' or 'RB-ILD' was coined by Myers and colleagues[4] to recognize the clinico-pathological entity of diffuse lung disease occurring in a series of heavy cigarette smokers in whom surgical lung biopsy revealed only respiratory bronchiolitis. In these specific instances, the lesion of respiratory bronchiolitis was not felt to be a mere indicator of exposure to smoking, but rather constituted the primary histopathological lesion responsible for diffuse lung disease. Subsequent reports described the clinico-pathological entity of RB-ILD as an interstitial and bronchiolar pulmonary process occurring in smokers in whom respiratory bronchiolitis was the only definable pathological abnormality present.[1,3,26]

The true prevalence of RB-ILD is difficult to estimate because some patients may be relatively asymptomatic, and symptoms in some smokers with diffuse lung disease may be attributed to chronic smoking itself ('smoker's cough').[5] The duration of exposure to cigarette smoke does not need to be prolonged or severe since some patients with RB-ILD have relatively limited smoking histories.[1] Most patients are relatively young adults between the ages of 30 and 60 years, and there is no gender predilection.[5,67] A clinical syndrome indistinguishable from RB-ILD has also been described in individuals exposed to solder fumes,[3] diesel smoke and fibreglass,[1] although these cases are exceedingly rare.

The usual presenting symptoms are chronic cough and dyspnoea, but an acute presentation has been described.[68] The physical examination yields nonspecific findings.[67] Digital clubbing is uncommon. Pulmonary function results may reveal obstructive, restrictive or mixed abnormalities with a reduction in diffusion capacity, but a substantial proportion of RB-ILD patients will have normal lung function at diagnosis.[5] Physiological impairment, when present at the time of clinical presentation, is typically mild to moderate.[5] A significant response to inhaled bronchodilator occurs in approximately 10% of affected individuals. Chest radiography reveals bilateral, fine reticular or reticulonodular opacities in over two-thirds of patients, but may be normal in up to 20% of patients.[3,5] The main CT scan abnormalities include bronchial wall thickening, fine centrilobular nodules and patchy areas of ground-glass attenuation.[3,5] The ground-glass changes are typically bilateral, patchy and affect both upper and lower lung fields (figure 1).[57,69] Emphysematous changes are frequently seen, as nearly all the patients with RB-ILD are current or former smokers. Honeycombing and fibrosis are unusual.

The differential diagnosis of RB-ILD is relatively broad and includes consideration of any of the con-

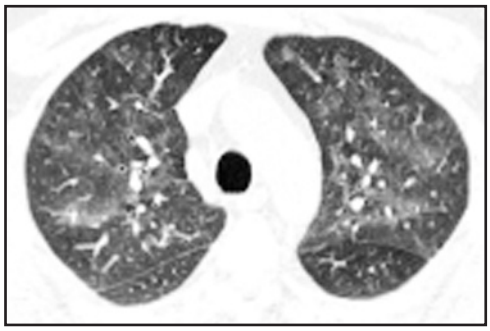

Fig. 1. Respiratory bronchiolitis-interstitial lung disease (RB-ILD). Chest CT scan showing patchy areas of ground-glass attenuation in upper lung fields in a smoker with biopsy-proven RB-ILD.

ditions associated with bronchiolar inflammation, including infectious, inflammatory (follicular bronchiolitis and hypersensitivity pneumonitis), aspiration-related bronchiolitis, talc pneumonitis and other rare lung conditions. Lung biopsy may provide a definitive diagnosis, but in routine clinical practice, a provisional diagnosis may be established on the basis of appropriate clinical and radiological features if other conditions that may mimic RB-ILD have been excluded.[3] Bronchoscopic lung biopsy has a low yield and bronchoalveolar lavage (BAL) findings are not diagnostic for RB-ILD. However, bronchoscopy and BAL may be diagnostically helpful in distinguishing RB-ILD from hypersensitivity pneumonitis or sarcoidosis, both of which are associated with BAL lymphocytosis and different histological features on biopsy.

The histopathological findings required for the diagnosis of RB-ILD are those of respiratory bronchiolitis. Although it might appear intuitive that RB-ILD is an exaggerated form of respiratory bronchiolitis, histopathological studies show that patients with RB-ILD have similar findings as those with respiratory bronchiolitis, and there are no reliable histopathological findings that can be used to differentiate the two.[70] The main histopathological features 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. [70] At low power, these features are patchy and generally confined to peribronchiolar regions (bronchiolocentric). Mild peribronchiolar fibrosis can be seen, but honeycombing is unusual.[3,69]

Smoking cessation is a key component of RB-ILD management. For patients with mild forms of disease, this may be the only therapeutic manoeuvre indicated. Smoking cessation may lead to improvement in radiological abnormalities and lung function.[5,71] The degree of improvement following smoking cessation appears to be limited in some patients and abnormalities may persist for decades.[1,37] For patients with significant lung impairment, corticosteroids are often employed, but without clear evidence of effectiveness.[5,37] Other immunosuppressive pharmacological strategies have been described, but there are no good data in support of the use of these agents in RB-ILD.[37] The prognosis for RB-ILD is relatively good and mortality from RB-ILD is uncommon.[5,37] Although smoking cessation may lead to disease remission in some patients with RB-ILD, longitudinal studies have shown that a significant number of patients remain symptomatic for years after smoking cessation.[37]

4. Desquamative Interstitial Pneumonia

Described by Liebow et al.[72] in 1965, DIP was originally believed to represent a lesion formed by desquamation of alveolar epithelial cells filling up the alveolar space, but was later recognized as an alveolar filling process characterized by macrophage accumulation in alveolar spaces.[72] Although classified as one of the 'idiopathic' interstitial pneumonias, DIP is clearly associated with cigarette smoking in at least two-thirds of patients.[5,26,28] Unlike RB-ILD, which is exceedingly uncommon in non-smokers, DIP has been described to occur in the context of autoimmune diseases,[47] certain infections[73] and following certain medication exposures,[73,74] implying that smoking is only one – albeit the most prevalent – of several potential factors associated with development of DIP. Also unlike RB-ILD, DIP has been reported to occur in children, although not in association with cigarette smoking.[5]

The clinical presentation of DIP is nonspecific and almost always chronic in onset.[5] Physical examination reveals inspiratory crackles in approximately 60% and digital clubbing in 25–50% of patients.[5] Pulmonary function testing reveals a restrictive ventilatory defect in one-third of patients, and a mixed defect is seen in another one-third of patients.[5] An obstructive pattern is rarely observed. As in RB-ILD and PLCH, pulmonary function tests can be normal in 10–20% of patients.[67] The degree of physiological abnormalities is generally more severe than those seen with RB-ILD.

The chest radiograph is abnormal in 80–90% of patients with DIP, typically revealing nonspecific abnormalities such as patchy ground-glass attenuation with lower zone predominance or nonspecific linear patterns.[75] The striking abnormality on chest high-resolution CT (HRCT) scans is ground-glass opacities predominantly in the lower lung zones and often in a peripheral distribution (figure 2).[76] Irregular linear opacities and reticular patterns are frequent, but honeycombing is rare. The HRCT findings in DIP can overlap with those of RB-ILD.[77] In only a few patients, DIP can progress to fibrosis where the HRCT scan has been described to be suggestive of fibrotic nonspecific interstitial pneumonia (NSIP).[67] Small parenchymal cysts and emphysematous changes may also be seen, especially in smokers.[77]

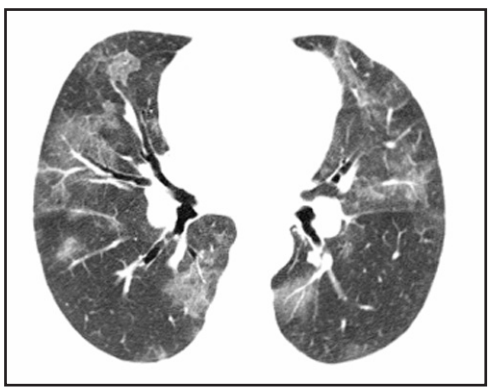

Fig. 2. Desquamative interstitial pneumonia (DIP). Chest CT scan showing patchy areas of ground-glass attenuation in a smoker with biopsy-proven DIP.

Histologically, DIP is characterized by filling of alveolar spaces with pigmented alveolar macrophages, as seen with RB-ILD.[28] However, there are a number of distinguishing features that help in differentiating DIP from RB-ILD.[28] While both RB-ILD and DIP are associated with the accumulation of pigmented macrophages in alveolar spaces, RB-ILD is characterized by bronchiolocentric, patchy distribution, whereas DIP is associated with diffuse involvement of pulmonary acini.[15] In addition, the extent of interstitial fibrosis, lymphoid follicles and eosinophilic infiltration tends to be more prevalent in DIP than RB-ILD.[26,28] There may be alveolar septal fibrosis and mild interstitial inflammation present, but honeycombing is unusual.[70,78] In contrast to UIP, fibroblast foci are not seen, and the DIP lesion is temporally uniform and not heterogeneous.[70] Bronchoscopic biopsy has a low diagnostic yield, and BAL findings are nonspecific, but may be helpful in excluding other conditions that mimic DIP. A definitive diagnosis of DIP can only be established by surgical lung biopsy, as it is often not possible to reliably differentiate DIP from NSIP or RB-ILD by clinical, radiological and bronchoscopic criteria.[15]

Since the majority of patients with DIP are smokers, smoking cessation is a cornerstone of therapy. Prolonged remission of DIP after smoking cessation has also been described.[79] Unlike RB-ILD, DIP can progress to respiratory failure.[80] In one series of 23 individuals with biopsy-proven DIP, three deaths from respiratory failure occurred, at 8, 13 and 40 months following the diagnosis of DIP.[28] DIP can gradually progress, particularly in those who continue to smoke. It has been suggested that in some patients, DIP progresses to a radiological pattern of fibrotic NSIP, but this has not been confirmed by histology. Patients with DIP are frequently treated with corticosteroids, but the success with corticosteroids is inconsistent.[5] In patients with severe or progressive disease, corticosteroids can be tried in the dosage range of 30–40 mg orally once daily and tapered slowly over 3–6 months.[81] Other immunosuppressants, such as azathioprine and methotrexate, have been employed in patients who

do not respond to corticosteroids.[81] Lung transplant remains an option in patients with progressive disease and severe respiratory impairment. DIP can recur in the transplanted lung.[82]

5. Pulmonary Langerhans' Cell Histiocytosis

PLCH (also referred to as pulmonary Langerhans' granulomatosis, eosinophilic granuloma or histiocytosis X) is characterized by abnormal accumulation of CD1a-expressing dendritic cells called 'Langerhans' cells' in the lungs and occasionally in other organ systems.[83,84] LCH also occurs in children, but pulmonary involvement in childhood LCH is quite uncommon, is usually not associated with smoking, and the pathobiology is probably distinct from adult LCH.[85] The adult form is seen almost exclusively in smokers and represents polyclonal proliferation of Langerhans' cells.[85] Adult PLCH forms part of the histiocytic disease spectrum, which ranges from relatively benign processes, such as focal LCH involving bone or skin, to disseminated and multi-systemic forms of LCH associated with aggressive disease course and high morbidity and mortality.[86] In contrast with DIP and RB-ILD, which exclusively affect the lungs, approximately 15% of adults with PLCH have extrapulmonary manifestations involving bone, skin, pituitary gland, liver, lymph nodes and thyroid gland.[6,87] Although an accurate estimate of prevalence is not available, PLCH may be the most common of the smoking-related diffuse lung diseases, representing around 5% of the total number of interstitial lung diseases diagnosed by lung biopsy.[87] PLCH tends to affect young individuals in their third and fourth decades.[6] Although historically PLCH was determined to be more prevalent in men,[88-91] more recent studies have found a slight preponderance in women,[2,6] which probably reflects social trends in tobacco use by women.

Approximately 95% or more of adults diagnosed with isolated PLCH are active or former smokers.[2,16,27,92] The pathogenesis of PLCH is poorly understood. Cigarette smoke may activate macrophages and epithelial cells to produce cytokines that promote Langerhans' cell recruitment and activation in sub-epithelial regions of the airways.[59,60,93] It is also possible that macrophages may be directly activated by certain cigarette smoke constituents, and produce cytokines like tumour necrosis factor-α that may subsequently activate dendritic and Langerhans' cells in the surrounding region.[83] Other cytokines abundant in the lungs of PLCH patients include TGFβ, another factor that is essential in the development of Langerhans' cells.[94] Additional factors in cigarette smoke, such as tobacco glycoprotein, may also be directly involved in immune cell activation in peribronchiolar regions and promote inflammatory nodule formation. Once activated, Langerhans' cells and macrophages may promote secondary recruitment of other inflammatory cells, including T cells, plasma cells and eosinophils, resulting in formation of loosely formed granulomas that centre around small airways (pathological correlate of nodules seen on HRCT scans).[83]

The presenting symptoms of PLCH are nonspecific, and primarily include dry cough and shortness of breath, while a portion of patients may be asymptomatic.[6] Constitutional symptoms occur in one-third of patients and 15% will experience a spontaneous pneumothorax, which may be recurrent.[6,95] Patients with disease outside the chest may have symptoms related to skin, lymph node, pituitary or bone involvement. Pulmonary function tests may show obstructive, restrictive, mixed or nonspecific abnormalities.[6] Early in the course of the disease, pulmonary function testing may be completely normal. Physiological studies reveal limitations in exercise capacity that can occur even with relatively normal resting pulmonary function in patients with PLCH. Exercise limitation correlates best with markers of pulmonary vascular dysfunction, implying vascular involvement rather than ventilatory impairment as a primary cause of exercise limitation in these patients.[96]

The chest radiograph is abnormal in most patients and reveals nonspecific findings.[97] Imaging of the chest with HRCT frequently shows characteristic abnormalities highly suggestive of PLCH. The predominant HRCT findings include bilateral per-

ibronchial nodules and cysts in varying combinations depending on when the HRCT scan is performed during the clinical course of the disease (figure 3). Nodules of different size with or without cavitation predominate in early disease, whereas cystic changes are more prevalent in advanced disease.[97,98] Advanced cystic changes may be difficult to distinguish from emphysema. Presence of bilateral nodules and cysts with sparing of bases in a smoker is highly suggestive of PLCH.[99]

A bronchoscopic or surgically obtained lung biopsy is recommended to confirm the diagnosis, but is not always indicated or necessary, particularly in minimally symptomatic patients. Bronchoscopy is diagnostically useful if elevated percentage of CD1a+ cells is identified in the lavage fluid, with ≥5% being virtually diagnostic of PLCH.[100-102] Patients with histologically documented LCH at an extra-pulmonary site (skin, bone, etc.) do not require lung biopsy to establish pulmonary involvement if the radiological features are consistent with the diagnosis.

Histological features of early PLCH include loosely formed nodules of mixed inflammatory cells around small airways in a bronchiolocentric pattern.[25] These bronchiolocentric lesions of PLCH typically form symmetric stellate lesions with central scarring.[70] 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.[16,70,85,102] Eosinophilic infiltration is often encountered, and may be quite extensive earlier in the course of the disease, hence the former term 'eosinophilic granulomas'.[16,70,85,102] Varying degrees of interstitial infiltration with macrophages, lymphocytes and eosinophils may accompany, and rarely, extensive alveolar macrophage infiltration causes a 'pseudo-DIP' reaction.[25] In some patients, PLCH is associated with extensive vascular infiltration of inflammatory cells, resulting in a proliferative vasculopathy that may be observed involving both arteries and veins.[103]

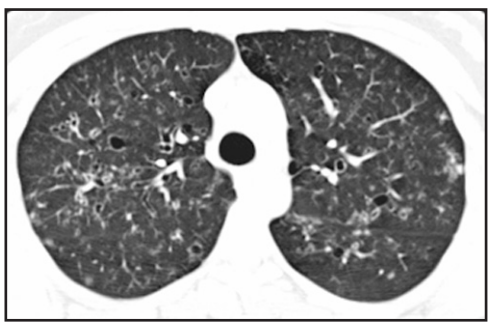

Fig. 3. Pulmonary Langerhans' cell histiocytosis (PLCH). Chest CT scan in a smoker with biopsy-proven PLCH demonstrating a combination of cystic and nodular lesions in both upper lung fields.

A critical component in the treatment of PLCH is smoking cessation. Smoking cessation often leads to stabilization of symptoms.[6,36,38,104] However, some individuals may show disease progression with subsequent respiratory failure despite smoking cessation.[6] There is no biological marker 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. Corticosteroids in the form of prednisone 40–60 mg/day with slow tapering over months have historically been employed to treat patients with severe or progressive disease, but the amount of data on objective therapeutic benefit of corticosteroids is limited.[87] Because of the perceived lack of effectiveness of corticosteroids, a number of other immunosuppressive agents, namely vinblastine, cladribine (chlorodeoxyadenosine; also known as 2-CDA),[105] cyclophosphamide and methotrexate, have been used to treat progressive PLCH.[87] Cladribine has been used in the management of multi-system LCH involving bone and skin with good success, but its utility in the management of smoking-related PLCH is not well defined.[105,106] Whether immunosuppressive therapy is effective in the management of patients with progressive disease who continue to smoke is not known.

Treatment of PLCH also includes the management of specific complications and sequelae such as recurrent pneumothorax, pulmonary hypertension and progressive respiratory failure.[6,83,95,103] Pneu-

mothorax is generally managed 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 measures is high.[95] Pulmonary hypertension, an important complication of PLCH, is present in all patients with advanced disease, and portends a poor prognosis.[92,103] We routinely perform a 2-dimensional ECG on patients with PLCH at the time of diagnosis and later in the clinical course if dyspnoea or the degree of hypoxaemia seem out of proportion to the severity of ventilatory impairment assessed by pulmonary function testing.[92] If the patient has ECG evidence of pulmonary hypertension, a right heart catheterization should be performed to confirm the presence and determine the severity of the condition, and assess response to vasodilator therapy. The use of vasodilators, such as the endothelin antagonist bosentan and the phosphodiesterase inhibitor sildenafil, should be considered in patients with moderate to severe pulmonary hypertension (personal observation). Overall, most patients seem to have a relatively good prognosis, particularly if smoking cessation is achieved. The overall median survival from time of diagnosis is approximately 13 years, with a 5-year survival of 74.6% and a 10-year survival of 63.9%.[92] Some individuals may progress to extensive pulmonary scarring and emphysematous changes leading to respiratory failure.[57,92] Lung transplantation is an option with advanced PLCH. The overall survival of PLCH patient with a lung transplant is comparable with that of individual with other indications for lung transplants.[39,107] Recurrence of PLCH in the transplanted lung even after smoking cessation has been described in a few patients.

6. Acute Diffuse Lung Diseases Precipitated by Cigarette Smoking

AEP is a form of acute respiratory failure associated with eosinophilic pulmonary infiltration. A number of causes have been described for AEP, including drugs,[108-111] toxins,[112] infections,[113,114] chemicals,[115] heavy metals[112] and cigarette smoke.[18,19,29] Multiple case series and reports of AEP illustrate a relationship to cigarette smoking and, particularly, recent-onset smoking,[29,43] or changes in smoking habits.[43] In 2004, a small outbreak of AEP in 18 patients occurred among 183 000 US military personnel deployed in or near Iraq from 2003 to 2004.[13] Most of these affected soldiers were between the ages of 19 and 47 years, and all were smokers.[13] Seventy-eight percent had started smoking within 2 weeks to 3 months prior to being diagnosed, and two soldiers reported increase in the quantity of cigarette smoking during the same time period.[13] Previous reports from Japan have also described recent-onset of cigarette smoking as a precipitant of AEP.[10,11,43]

The exact pathogenesis of AEP is unknown, but increased levels of IL-5 and IL-18 in BAL fluid suggest a possible role of T_h2 cells as mediators of eosinophil and T-cell recruitment and inflammation. Cigarette smoke is known to suppress the production of the T_h1 polarizing cytokine IL-12 and facilitates the generation of T_h2 priming cytokines *in vitro*,[45] suggesting that acute cigarette smoke exposure may promote stimulation of T_h2 inflammatory responses that enable recruitment and activation of eosinophils in the lungs.[113] Eosinophilic infiltration may subsequently promote direct damage to lung tissue by release of soluble factors in eosinophilic granules.[113]

AEP is distinct from other smoking-related diffuse lung diseases because it is acute in onset and can occur in the absence of cigarette smoke exposure in a substantial proportion of patients. Symptoms at presentation are nonspecific, and include acute dyspnoea and cough that rapidly progress over a 7- to 14-day period. During the acute illness, the chest radiograph shows bilateral pulmonary reticular infiltrates with Kerley-B lines[108] and small pleural effusions.[116] Parenchymal infiltrates can progress to mixed reticular and alveolar patterns. Chest HRCT reveals patchy bilateral alveolar infiltrates, diffuse interstitial infiltrates or diffuse bilateral ground-glass opacities with pleural effusions.[116]

In the proper clinical context, BAL with more than 20% eosinophils establishes the diagnosis.[117]

The presence of more than 20% neutrophils and up to 15% lymphocytes is also helpful in differentiating acute from chronic eosinophilic pneumonia.[117,118] An increase in serum and BAL levels of surfactant protein-D has been reported as a marker of AEP.[119,120] The peripheral eosinophil count may be normal at presentation, but is commonly elevated later in the clinical course.[121] Transbronchial biopsy reveals marked eosinophilic infiltration in the interstitium and the alveoli. The alveolar architecture is preserved, but there can be changes of acute respiratory damage in terms of hyaline membrane formation, fibroblast proliferation and presence of other inflammatory cells.[122]

The clinical picture of AEP is similar to that of acute respiratory distress syndrome (ARDS).[42,123] Corticosteroid therapy is effective; pulmonary filtrates and effusions usually resolve rapidly and recurrence is unusual.[117] Few deaths due to refractory ARDS, and failure to recognize and treat AEP in a timely fashion have been reported.[13,123] There are a few reports of spontaneous resolution of AEP.[124] Smoking cessation should be strongly advised for patients with smoking-related AEP. Most patients have no long-term sequelae from AEP; however, some patients have reported dyspnoea on exertion with mild restrictive lung disease even after 1 year.[121]

Cigarette smoking is also implicated as a precipitant of acute pulmonary haemorrhage in patients with Goodpasture's syndrome, an inflammatory pulmonary-renal syndrome associated with circulating anti-glomerular basement membrane (anti-GBM) antibodies.[20,125] In one study, it was reported that, out of 51 patients with glomerulonephritis associated with anti-GBM antibodies, pulmonary haemorrhage occurred in all cigarette smokers compared with only 20% of the non-smokers.[20] In addition, resumption of smoking was followed by recrudescence of lung haemorrhage in one patient.[20]

7. Cigarette Smoking and Other Interstitial Lung Diseases

There are other interstitial lung diseases that are more prevalent in cigarette smokers, but the cause-effect relationship is not well defined. There are a number of studies that have shown UIP, the pathological lesion identified in patients with idiopathic pulmonary fibrosis, to be more common amongst smokers. But there are no compelling data indicating that cigarette smoking directly causes lung fibrosis or UIP.[126] It is conceivable that cigarette smoke might act as a co-factor along with some other unknown environmental or endogenous pro-fibrotic stimuli in susceptible individuals and promote development of UIP. Smoking also appears to influence the natural course of UIP.[127] A study on survival in UIP patients showed that current smokers with UIP may have a survival advantage compared with UIP patients who quit smoking or never smoked.[127] This so-called 'protective effect' of smoking was brought into question by a recent study of 249 patients with idiopathic pulmonary fibrosis in whom severity adjusted survival was higher amongst those who had never smoked.[128] Cigarette smokers are also at increased risk of developing rheumatoid arthritis and individuals with established rheumatoid arthritis are at higher risk of developing interstitial lung disease than non-smokers. A study of 336 patients with rheumatoid arthritis found that those with a >25 pack-year smoking history were significantly more likely to have radiological evidence of diffuse lung disease (odds ratio [OR] 3.76; 95% CI 1.59, 8.88).[21] Cigarette smoking is likely to represent the principal preventable risk factor for rheumatoid arthritis-associated interstitial lung disease.

8. Interstitial Lung Diseases that Appear to be Less Prevalent in Active Smokers

The fourth group of interstitial lung diseases proposed in table I are distinguished by the fact that they are less prevalent in active smokers compared with non-smokers.[14,33,129,130] Hypersensitivity pneumonitis is an allergic immune-mediated interstitial and small airway disease that may be in-

duced by exposure to many different antigens in the environment. Potential mechanisms by which cigarette smoking may limit development of hypersensitivity pneumonitis in predisposed individuals include inhibition of macrophage and dendritic cell co-stimulatory capacity,[24,45] suppression of cytokines such as IL-12 by activated dendritic cells[45] and suppression of T-cell function.[131] The recognition that smoking may reduce the occurrence of hypersensitivity pneumonitis should never be used as evidence in favour of tobacco use in individuals with hypersensitivity pneumonitis. Although less prevalent in active smokers, hypersensitivity pneumonitis can and does occur in current smokers and in those who have recently quit smoking.[132] In one study that compared the clinical features of hypersensitivity pneumonitis in smokers and non-smokers, recurrent symptoms following diagnosis and vital capacity measurements were worse in smokers.[132] In addition, smokers with hypersensitivity pneumonitis had a worse prognosis, with a 10-year survival of 70.7% compared with 91.5% in non-smokers.[132]

Sarcoidosis is the second condition in this group of conditions that are less prevalent in smokers.[31] In a large case control study on aetiological factors in sarcoidosis, a history of ever having smoked cigarettes was less frequent among the 706 subjects with sarcoidosis than control subjects (OR 0.62; 95% CI 0.50, 0.77).[133] Potential mechanisms by which cigarette smoke may limit granulomatous inflammation in sarcoidosis include the suppression of T_h1 cytokines by macrophages and dendritic cells,[45] and suppressive effects on T-cell function. 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 non-smokers with sarcoidosis.[23,134] Interestingly, smokers are at increased risk of developing tuberculosis,[135-137] an infectious disease that requires granuloma formation for mycobacterial containment. It is tempting to speculate that the mechanisms by which smoking impairs granulomatous inflammation in sarcoid may be responsible for the observed increased predisposition to tuberculous disease in smokers.

9. Conclusion

Substantial evidence implicates cigarette smoking as the principal aetiological factor responsible for the development of RB-ILD, DIP and PLCH. Cigarette smoking is an important precipitant of AEP and lung haemorrhage in patients with Goodpasture's syndrome, and smokers are at higher risk of developing idiopathic pulmonary fibrosis and rheumatoid-associated interstitial lung disease. It is important to recognize and continue to investigate the role of cigarette smoke in the pathogenesis and natural history 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,[138] it is likely that the burden of tobacco-related diseases, including tobacco-induced diffuse lung diseases, will become more prevalent. Practitioners should utilize and recognize smoking cessation strategies as a critical component of therapy for these patients, with corticosteroids and other immune-modifying agents as adjunctive treatments.

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