Smoking-related Interstitial Pneumonias and Pulmonary Langerhans Cell Histiocytosis

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The relationship between cigarette smoke and interstitial lung diseases (ILDs) is not clear. Respiratory bronchiolitis (RB), usually found as an incidental histologic abnormality in otherwise asymptomatic smokers, is characterized by the accumulation of cytoplasmic golden-brown–pigmented macrophages within respiratory bronchioles. A small proportion of smokers have a more exaggerated response that, in addition to the bronchiole-centered lesions, provokes interstitial and air space inflammation and fibrosis extending to the nearby alveoli. This set of histologic changes is called RB-ILD, and results in clinical symptoms. Desquamative interstitial pneumonia (DIP) is characterized by panlobular involvement, diffuse mild-to-moderate interstitial fibrosis, and massive alveolar filling with macrophages. It is well known that the histopathologic patterns of RB-ILD and DIP may overlap, and that the key features for differentiating these disorders are the distribution and the extent of the lesions: bronchiolocentric in RB-ILD and diffuse in DIP. It has been proposed that RB, RB-ILD, and DIP may be different components of the same histopathologic disease spectrum, representing various degrees of severity of the same process caused by chronic smoking, although this is still controversial. Pulmonary Langerhans' cell histiocytosis is also strongly related to cigarette smoking and is characterized by the proliferation of specific histiocytes, known as Langerhans' cells, and their infiltration of organ systems. Although RB, RB-ILD, DIP, and Pulmonary Langerhans' cell histiocytosis are considered as discrete entities of smokers, it is not infrequent to find a mixture of pathologic features rendering the histopathologic diagnosis difficult.

Keywords: desquamative interstitial pneumonia; idiopathic interstitial pneumonias; pulmonary Langerhans cell histiocytosis; respiratory bronchiolitis–interstitial lung diseases; smoking-related interstitial lung diseases

Smoking-induced lung diseases constitute a complex group of disorders, varying from the well-known entity of chronic obstructive pulmonary disease (COPD) to the more recently described interstitial lung diseases (ILDs) (1, 2).

Cigarette smoke is a complex mixture of more than 6,000 compounds and causes a variety of pulmonary and systemic effects in humans (3, 4). Smoking remains the most preventable cause of premature death and morbidity in the United States and throughout the developed world (3, 4). Cigarette smoking is the major cause of lung cancer, which in turn is the leading cause of cancer deaths in both males and females in the United States (3, 4). In addition, cigarette smoking is the principal risk factor for developing COPD. An estimated 10 to 15% of all smokers develop clinically significant airflow obstruction (3). Recently, smoking has been implicated in causing ILD but this important relationship has not yet been well characterized: first, the various smoking-related ILDs are individually and collectively quite uncommon; second, there is considerable overlap between the presenting clinical signs and symptoms, pulmonary function parameters, radiographic findings, and, occasionally, even the histopathologic features of these diseases and much more common smoking-related lung conditions, such as chronic bronchitis and emphysema. This overlap may confound the interpretation of the clinical evaluation, potentially leading to an inaccurate diagnosis.

Cigarette smoking is associated with a variety of nonneoplastic histologic and radiographic changes in the lung (5–8). In some smokers, combinations of various patterns of injury can be identified in the same individual (9). Respiratory bronchiolitis (RB) is an incidental histologic abnormality in otherwise asymptomatic smokers. Smoking-related ILD is a term used to describe the relationship between RB-associated ILD (RB-ILD), desquamative interstitial pneumonia (DIP), and pulmonary Langerhans' cell histiocytosis (PLCH) as interstitial disorders that are etiologically linked to cigarette smoking (10). The pathogenic mechanisms that link tobacco smoke exposure to these disorders have not been elucidated (11). It is likely that these disorders occur in susceptible individuals following an initial injury to the bronchiolar and alveolar epithelium. Patients with PLCH have an abnormal T-cell proliferative response to tobacco glycoproteins (12) and an increased secretion of bombesin-like peptides from neuroendocrine cells in the lung. The microscopic evidence of alveolar-wall destruction in patients with RB gives support to the argument that this type of bronchiolitis may be a precursor of centrilobular emphysema (13). DIP and RB-ILD are currently classified as forms of idiopathic interstitial pneumonia (14), although some authors do not consider these two entities to be idiopathic but secondary to smoking (15).

Below, we consider each of the smoking-related ILD individually. Although there is currently a lively debate on the relationship between DIP and RB-ILD, and, in particular, whether they represent different points along the spectrum of the same disease (2, 9, 14, 16, 17), we present these diseases separately. Furthermore, although epidemiologic studies have suggested that there is some relationship between smoking and idiopathic pulmonary fibrosis, the clinical entity associated with the pathologic diagnosis of usual interstitial pneumonia (UIP) (5), this association is less strong than for PLCH, DIP, and RB-ILD, and therefore we do not discuss idiopathic pulmonary fibrosis further.

DIP

DIP is an uncommon form of interstitial pneumonia. It was first described by Liebow and colleagues (18) in 1965, and ever since there has been extensive debate regarding its relationship to UIP. It was previously considered that DIP was the early, cellular phase and UIP the later, fibrotic phase of the same disease (19, 20) but they are now accepted as separate clinical-pathologic entities. The term "desquamative interstitial pneumonia" is a morphologic description but is a misnomer because the dominant

histologic feature is intraalveolar macrophage accumulation rather than desquamated pneumocytes.

Epidemiology

There are very few studies describing the epidemiology of DIP. The incidence and prevalence of DIP are not known. In the two largest case series (15, 21), involving 36 and 40 patients, the mean age of onset of symptoms leading to a diagnosis of DIP was 42 yr. In a recent study (22), the mean age at diagnosis was 46 yr. A history of smoking has been demonstrated in about 90% of patients with DIP (20–22). DIP is occasionally associated with other conditions, including connective tissue diseases, drug reactions, and environmental exposures (15, 21, 22). In addition, a focal accumulation of macrophages, termed a "DIP-like reaction," may be seen as an incidental lesion in a number of settings (23–25). A lesion resembling DIP has been described (26) in infants with mutations in the gene encoding surfactant protein C; this condition is distinctly different from DIP in adults.

Clinical Features

Dyspnea, at rest or with exertion, is the most common complaint in patients with DIP. This symptom is reported by 85 to 100% of patients and is usually the reason why such patients seek medical attention (15, 18, 21). Cough, which may be either nonproductive or associated with nonpurulent sputum, is also quite common, affecting 75 to 80% of patients with DIP (15, 18, 21, 22). Systemic symptoms are normally absent. The onset of symptoms is usually insidious. Physical examination of the chest reveals rales in half or fewer of patients (15, 21, 22). Interestingly, and unique among the smoking-related ILDs, clubbing appears to be a relatively frequent finding in DIP, occurring in nearly one-half of patients (21, 22, 27). Laboratory investigations are usually unremarkable.

The most common and striking abnormality shown by pulmonary function tests (PFTs) in patients with DIP is a marked reduction in carbon monoxide diffusing capacity ($D_{L_{CO}}$) (15, 21). Patients with DIP almost never have a normal $D_{L_{CO}}$ and commonly display reductions of 50% or more from the predicted value. Patients with advanced disease may have severe hypoxemia, either at rest or with exertion. Significant airflow obstruction is rather uncommon although a restrictive ventilatory defect is present in approximately half of the patients with DIP (15, 21, 22).

Radiographic Findings

Conventional chest radiographs are rarely normal (15, 21, 22, 28). The predominant findings on chest radiographs and high-resolution computed tomography (HRCT) are bilateral symmetric areas of ground-glass opacification involving mainly the lower lung zones (18, 28–30). Mild, localized areas of fibrosis cause a reticular pattern that can be seen on the radiograph and on CT in approximately 50% of patients (21, 22, 28). Fibrosis is usually limited to the subpleural regions of the lower lung zones (Figure 1). The areas of ground-glass attenuation seen on HRCT have a predominantly peripheral distribution in 60% of patients, have a patchy distribution in 25%, and are diffuse in 15% (Figures 2 and 3) (28). In the majority of cases, treatment improves or resolves the areas of ground-glass attenuation (28). In approximately 20% of cases, the areas of ground-glass attenuation progress to a reticular pattern, reflecting the presence of fibrosis (28, 31).

Histopathologic Findings

The main histologic finding in DIP is the presence of increased numbers of macrophages within alveolar spaces (18, 21, 25). This abnormality is usually quite striking, but in early cases, can be a subtle finding. There is often associated interstitial fibrosis, which varies in degree from case to case, but inflammation is minimal. The interstitial changes are, however, always overshadowed by the airspace macrophage accumulation (Figure 4). Alveolar pneumocyte proliferation may be prominent along the thickened alveolar septa, but fibroblastic foci do not occur. At low magnification, the process typically seems to affect the lung diffusely and appears uniform from field to field (25). Bronchoalveolar lavage (BAL) fluid contains increased numbers of alveolar macrophages with granules of "smoker's pigment" (golden-brown pigment–laden macrophages) (32); Prussian blue staining for iron can reveal a finely granular hemosiderin pigment.

Diagnosis, Treatment, and Outcome

The diagnosis of DIP should be considered whenever the clinical presentation (dyspnea, cough, clubbing), epidemiologic features (smoker, adult aged 40 to 60 yr), and initial diagnostic studies (decreased $D_{L_{CO}}$ in PFTs; symmetric bilateral, reticular, or ground-glass opacities on chest radiography) are typical. When reasonable doubt about the diagnosis remains, thoracoscopic lung biopsy is recommended (14, 17). Lung biopsy is important for ruling out more aggressive forms of ILD.

Smoking cessation is currently considered the primary treatment for DIP and should be promoted as strongly as possible because it often leads to regression of the disease (33, 34). Most patients with DIP are treated, usually with oral corticosteroids such as prednisone at a standard dose of 40 to 60 mg daily. Although no randomized trials have demonstrated the effectiveness of this therapy, it is generally recommended for patients with significant symptoms, PFT abnormalities, or chest HRCT findings, as well as for aggressive disease. Treatment should be continued at the starting dose for 1 to 2 mo, and then an attempt should be made to gradually taper off the medication over 6 to 9 mo (17). Careful monitoring of the patient's respiratory status and potential steroid complications is recommended. A higher percentage of patients with DIP respond to steroid therapy than do patients with UIP; approximately two-thirds of patients with DIP show stabilization or improvement of symptoms (15, 21). The role of cytotoxic and other immunosuppressive agents remains undefined.

The 5- and 10-yr survival rates are 95.2 and 69.6%, respectively, for patients with DIP (21). Nevertheless, DIP progresses in some cases and a small number of patients have a poor outcome (31). Lung transplantation has been performed successfully in patients with end-stage disease; however, disease recurrence in the transplanted lung has been reported (35).

RB-ILD

The macrophage accumulation in DIP is often accentuated within peribronchiolar airspaces, but when the macrophage accumulation is confined to these areas with sparing of more distal airspaces, the process is termed RB-ILD (14). RB-ILD is considered a variant of DIP and is a patchy rather than a diffuse process, localized to peribronchiolar parenchyma. This term is derived from RB, a common incidental finding in cigarette smokers, characterized by the accumulation of pigmented macrophages within respiratory bronchioles, without significant accompanying ILD (36). RB originated as a term limited to an asymptomatic state; however, numerous reports have now described patients with respiratory symptoms and abnormal PFT or chest radiography in whom RB was the only definable pathologic abnormality present; the designation RB-ILD is applied to these patients (10, 37). In RB-ILD, interstitial thickening similar to that seen in DIP accompanies the airspace changes but is confined to the peribronchiolar parenchyma. Nonetheless, defining

Figure 1. Chest radiograph of a patient with desquamative interstitial pneumonia (DIP) showing bilateral interstitial infiltrates involving mainly the lower lung zones. Mild, localized areas of fibrosis cause a reticular pattern.

Figure 3. Coronal reconstruction of a case of DIP. There are bilateral areas of ground-glass and reticular opacities. The diagnosis of DIP was proven by open lung biopsy. (Courtesy of Professor A. Pesci, University of Parma.)

precisely who should be considered to have RB-ILD remains a significant challenge.

Clinical and Radiologic Findings

Most patients with RB-ILD have mild symptoms of dyspnea and cough. The disease usually affects current smokers 30 to 40 yr old with a history of more than 30 pack-years of cigarette smoking (10). PFTs demonstrate a reduction in $D_{L_{CO}}$, as well as airway obstruction and restriction (10, 15, 22, 38). Chest radiography reveals thickening of the walls of the central and peripheral bronchi and areas of ground-glass opacity (2). RB-ILD often manifests with the following characteristics on CT scans: centrilobular ground-glass nodules, thickening of central and peripheral airways with associated centrilobular emphysema, and air-trapping (2, 10, 39); rarely, a tree-in-bud pattern is present (40). These findings appear predominantly in the upper lobes (2, 10).

Histopathologic Findings

By definition, the pathologic findings in RB-ILD are fundamentally indistinguishable from those in RB (13) and differ more

Figure 2. High-resolution computed tomography (HRCT) of a patient with DIP, demonstrating bilateral areas of ground-glass opacity. (Courtesy of Professor A. Pesci, University of Parma.)

in degree than in kind from those seen in DIP (6). The most characteristic abnormality is a patchy accumulation of pigment-laden macrophages within the lumens of respiratory bronchioles and neighboring alveolar ducts and air spaces (Figure 5) (6). RB-ILD should be considered within the differential diagnoses whenever DIP is under consideration.

BAL fluid contains alveolar macrophages with golden, brown, or black pigment inclusions, findings that are indistinguishable from those seen in nonaffected smokers (32, 41).

Diagnosis, Treatment, and Outcome

The diagnosis of RB-ILD requires the proper clinical setting (specifically, a patient with a history of cigarette smoking within the last 6 mo), appropriate clinical and radiologic manifestations, and a lung biopsy that identifies RB-ILD and rules out more serious causes of diffuse ILD (2, 10). BAL is not routinely indicated. Transbronchial biopsy is not useful in distinguishing RB-ILD from DIP, a distinction with potential prognostic importance. Thus, unless the clinician is considering hypersensitivity pneumonia or sarcoidosis as possible differential diagnoses, transbronchial biopsy is not generally recommended. The decision to proceed to thoracoscopic lung biopsy must be considered when significant diagnostic uncertainty remains, the patient has substantial symptoms, or there are marked radiographic or PFT abnormalities.

Whether and how to treat RB-ILD is a difficult question, especially in the light of the condition's rather benign prognosis. Smoking cessation should be encouraged, although specific data on the benefits of such cessation are lacking for RB-ILD (as opposed to other smoking-related pulmonary diseases). Corticosteroids have been employed in various published series describing RB-ILD (15, 38), without any convincing evidence of effectiveness. Thus, unless the patient's symptoms or pulmonary function and radiographic abnormalities are extremely severe, smoking cessation and careful observation should form the basis of initial therapy. Only those who are profoundly affected or who progress despite successful smoking cessation should be considered as possible candidates for corticosteroids.

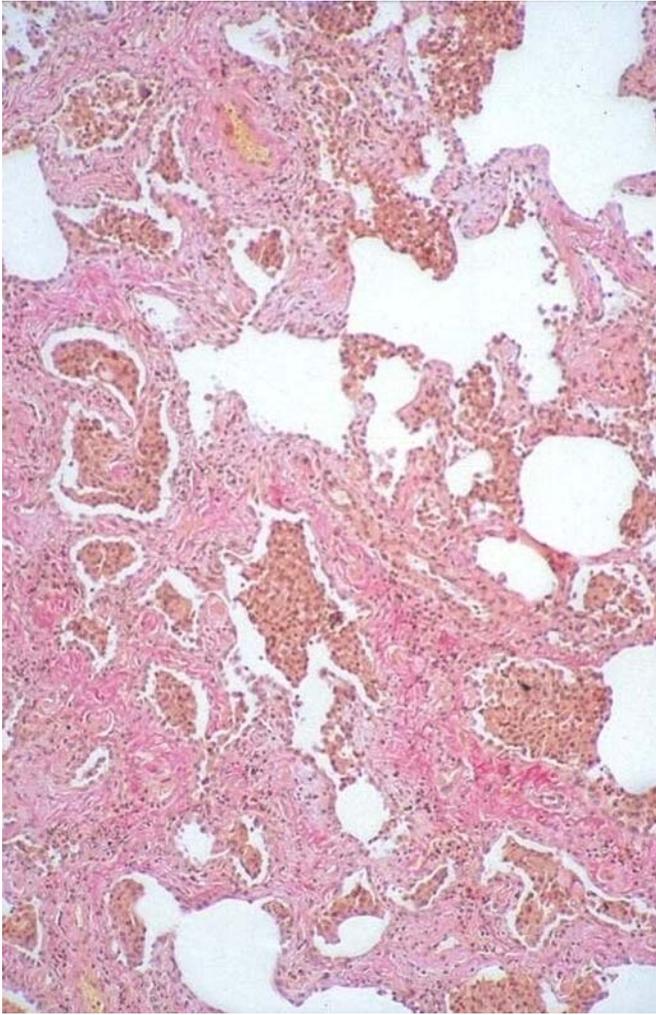No documented deaths or cases of respiratory failure have ever been attributed directly to RB-ILD.

Figure 5. Respiratory bronchiolitis in a patient with respiratory bronchiolitis associated interstitial lung disease: faintly pigmented alveolar macrophages fill the lumen of this respiratory bronchiole and the surrounding airspaces. The surrounding parenchyma is not involved. (Courtesy of Professor A. Pesci, University of Parma.)

Figure 4. Histopathologic specimen from a patient with DIP. There is diffuse, marked, intraalveolar accumulation of macrophages. Minimal interstitial fibrosis is present and the architecture of the lung is preserved. The changes appear uniform from field to field. (Courtesy of Professor A. Pesci, University of Parma.)

PLCH

PLCH is a rare and essentially sporadic disorder characterized by a proliferation of Langerhans' cell infiltrates that form multiple, bilateral, interstitial, peribronchiolar nodules, which frequently cavitate (30). Lung involvement may occur either in isolation or as part of a multiorgan disease (42).

Epidemiology

The precise incidence of PLCH is unknown, and is difficult to determine because the process can be asymptomatic and resolve spontaneously. PLCH accounts for fewer than 5% of ILDs diagnosed by surgical lung biopsy (43). It is especially common in young adults, with a peak incidence at 20 to 40 yr of age. Several studies have consistently shown that more than 90% of patients with PLCH are current or previous cigarette smokers (44). Smoking has been demonstrated to be a strong risk factor for development of this disease (45, 46). Furthermore, the bronchiolar distribution of the pathologic lesion is consistent with the possibility that an inhaled antigen is involved in the pathogenesis of this disorder. Children with Langerhans' cell histiocytosis
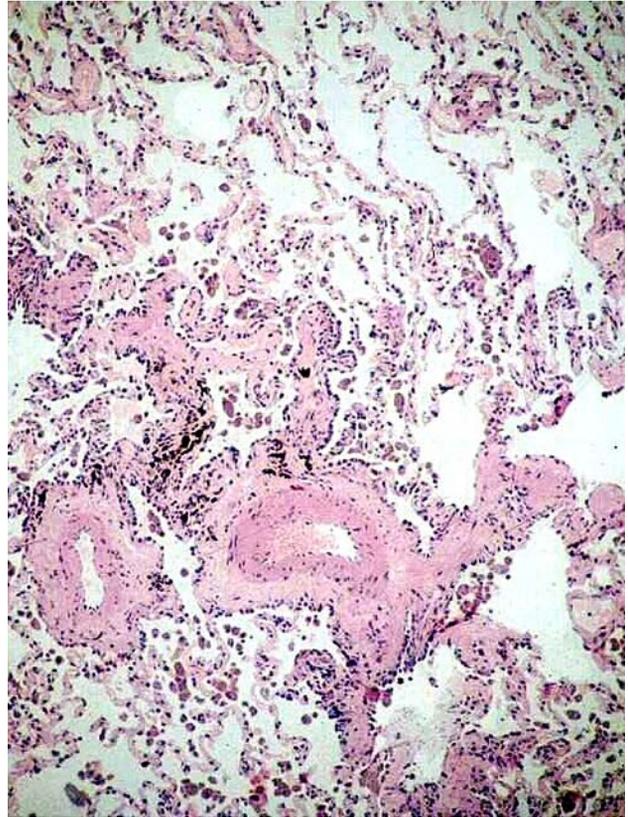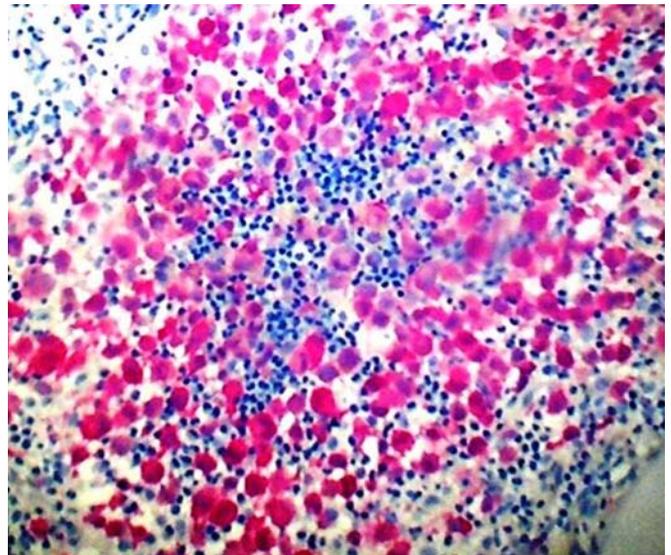

Figure 6. S-100–positive cells in a bone biopsy from a patient with an extrapulmonary localization of pulmonary Langerhans' cell histiocytosis (PLCH). Langerhans' cells express the cytoplasmic S-100 protein. The patient had pulmonary nodules on chest CT and a lytic lesion of a vertebral body.

occasionally manifest pulmonary involvement, but the disseminated nature of their disease suggests that it likely is a disease distinct from isolated PLCH, not smoking related (47).

Clinical Features

The clinical presentation of PLCH varies; dyspnea, cough, and chest pain are predominant symptoms (44, 48). Approximately 25% of patients are asymptomatic, and the disease is uncovered on a routine chest radiograph. Constitutional symptoms (fever, fatigue, night sweats, anorexia, weight loss) and hemoptysis can occur (44, 48). In 10% of cases, PLCH presents with spontaneous pneumothorax, which can be bilateral or recurrent (49). In adult patients with PLCH, bone lesions (skull, ribs, and pelvis) (Figure 6), pituitary involvement producing diabetes insipidus, and lesions of the skin are the most common extrapulmonary manifestations (44, 50, 51). Physical examination is often normal (44).

On PFT, the most frequently observed abnormality is a reduction in $D_{L_{CO}}$. Restrictive, obstructive, and mixed patterns have been described (42, 44, 50, 51). Exercise performance is commonly impaired and may reflect pulmonary vascular dysfunction (44, 52).

Radiographic Findings

In patients with PLCH, typical findings on chest radiographs include nodular or reticulonodular opacities most prominent in the middle and upper lung zones (Figure 7) (44). There is usually sparing of the costophrenic angles and the lung volume appears normal or increased. HRCT of the chest confirms the predominant upper lung involvement with relative sparing of the lung bases (42, 44). Thin-walled cysts, nodules (with or without cavitation), or a combination of nodules and cysts may be seen. In the later stages, nodular lesions tend to be less frequent, and cystic changes become more prominent (Figure 8) (42, 53). The shape of the cysts may be irregular and more complex than those seen in pulmonary lymphangiomyomatosis. The sparing of the lung bases is also an important finding in differentiating PLCH from pulmonary lymphangiomyomatosis (42, 48). The presence of typical features on HRCT frequently allows the clinicians to make a diagnosis of PLCH without lung biopsy.

Histopathologic Findings and Diagnosis

Morphologic confirmation of the diagnosis may be obtained by BAL, transbronchial biopsy, or surgical lung biopsy. The presence of increased numbers of Langerhans' cells in the BAL fluid (identified by staining with antibodies against CD1a, antigen on the cell surface) is strongly suggestive of PLCH (42). If a threshold of 5% of CD1a-stained cells is used for the diagnosis, the specificity of the test is good, but the sensitivity appears to be low (54). An indeterminate elevation in the percentage of CD1a-positive cells (2–5%) is found in the BAL in many cases. CD1a cells in this range may be present in heavy smokers and
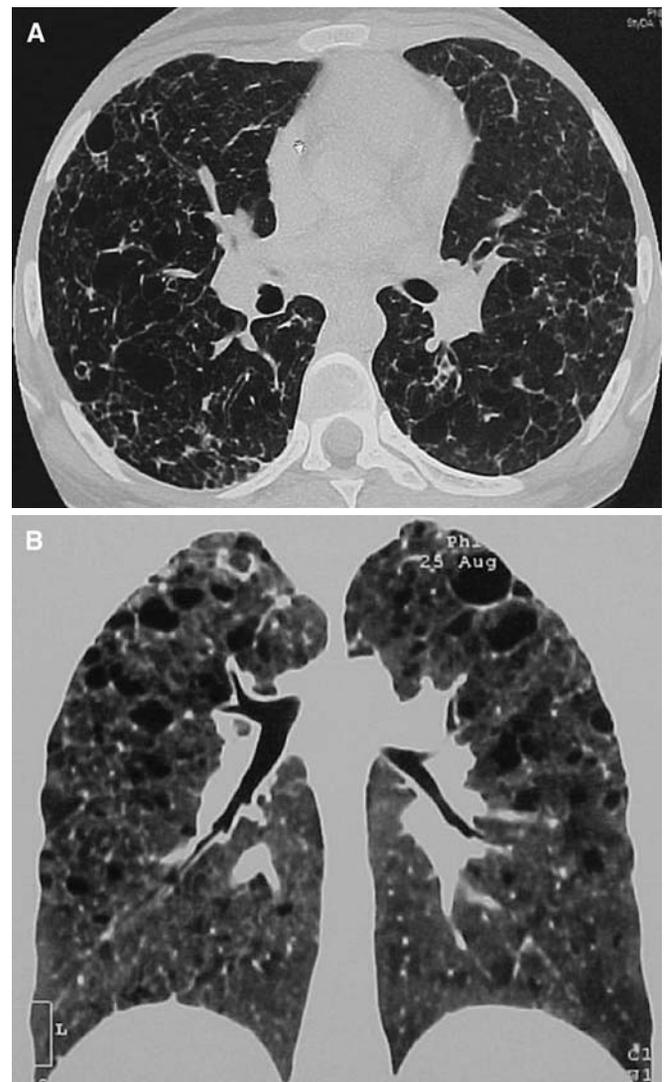

Figure 7. Chest radiograph of a patient with PLCH. The lung volume is preserved. Note the presence of a diffuse reticulonodular pattern superimposed on multiple cysts.

Figure 8. (*A*) HRCT shows extensive cystic lung disease in PLCH. Note the presence of bizarre-shaped cysts associated with deranged lung architecture. (*B*) Coronal reconstruction of a case of PLCH. HRCT of the chest confirms the predominant upper lung involvement with relative sparing of the lung bases.

in people with other ILD (e.g., sarcoidosis), making a low-level rise in the number of CD1a cells difficult to interpret with certainty. Transbronchial biopsy has a low diagnostic yield, ranging from 10 to 40% (42, 50), because of the patchy nature of the disease and the small amounts of tissue obtained. Surgical lung biopsy has the highest diagnostic yield (42, 50). Histologically, early PLCH lesions are characterized by cellular interstitial infiltrates composed of Langerhans' cells, lymphocytes, macrophages, eosinophils, plasma cells, and fibroblasts (48, 55). These infiltrates enlarge to form nodules centered on small airways (Figure 9) (48, 55). Cavitation within nodules represents either an airway remnant or *de novo* cavitation due to an enlarging inflammatory infiltrate (56). The histologic lesions progress from cellular nodules, to cellular and fibrotic nodules, to entirely fibrotic nodules that are often stellate in configuration and may connect with nodules in adjacent lung parenchyma. This process produces a distinctive honeycomb-like structure with enlargement of the airspaces and hyperinflation (50, 55). In any given specimen, lesions of different ages are seen (48). End-stage PLCH is characterized by prominent fibrotic scars and Langerhans' cells may be entirely absent.
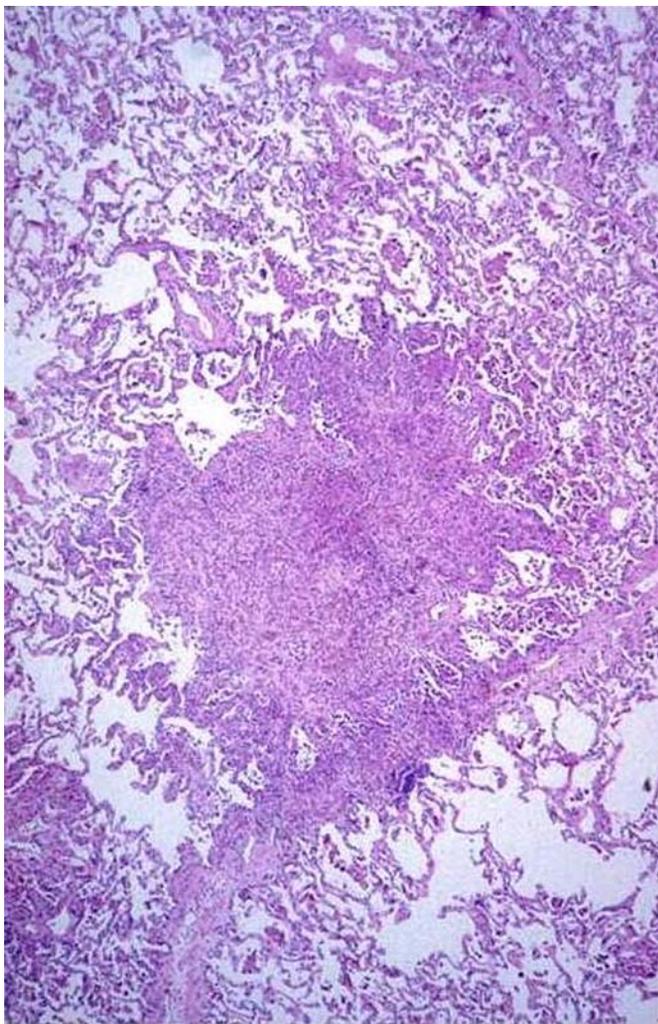

Figure 9. Nodular infiltrates with a stellate border extending into the surrounding interstitium in a patient with PLCH. (Courtesy of Professor A. Pesci, University of Parma.)

Treatment and Outcome

The evolution of PLCH is quite variable. Because of the wide variation in the natural history of PLCH, there are few reliable guidelines concerning treatment and prognosis. In general, the extent and severity of initial pulmonary involvement, as assessed by chest radiography and PFT, appear to have prognostic value (50, 57, 58). Progression of the disease to advanced pulmonary fibrosis and death are uncommon (50, 58). Patients with advanced PLCH can develop severe pulmonary hypertension (59, 60). Radiologic improvement and even complete resolution of PLCH after smoking cessation has been described in case reports (42, 61). Smoking cessation may prevent progression of the disease and should be strongly encouraged. Although corticosteroid therapy has been used in the treatment of patients with PLCH, its benefit is unclear (42, 50, 57, 58).

Chemotherapeutic agents such as vinblastine, cyclophosphamide, chlorambucil, methotrexate, etoposide, and cladribine have been used in patients with progressive disease that is unresponsive to corticosteroids or in those with multiorgan involvement. Unfortunately, none has clearly improved the course of the disease (42, 50, 57, 58). Because of the limited data on their efficacy, these drugs should be reserved as salvage therapy for patients with progressive disease that is unresponsive to both smoking cessation and a trial of corticosteroid therapy (42). Pleurodesis may be needed in patients with recurrent pneumothoraces.

Lung transplantation should be considered for patients with advanced disease associated with severe respiratory impairment and limited life expectancy or severe pulmonary hypertension (42). In several cases, however, PLCH has subsequently recurred in the transplanted lung (62).

CONCLUSIONS

The relationship between cigarette smoke and ILD is not yet clear. There is strong evidence supporting a potential causal role of cigarette smoke in the development of some ILDs, such as RB-ILD, DIP, and PLCH. These three ILDs are now often referred to as "smoking-related ILD." This term suggests that PLCH, DIP, and RB-ILD may form a spectrum of patterns of interstitial lung injury that may occur in predisposed individuals who smoke (5, 10, 14). These entities can represent different degrees of severity of small airway and parenchymal reaction to cigarette smoke or other environmental exposures (20). Although the pathogenic mechanisms linking tobacco smoke to these disorders have not been elucidated, there is growing evidence that the primary target in all these diseases is the terminal or respiratory bronchioles (11). The profusion of macrophages in the airspaces may be regarded as an idiosyncratic reaction to cigarette-smoke exposure (41). It has been proposed that increased production of bombesin-like peptides plays a central role in the pathogenesis of PLCH (42). Bombesin is a neuropeptide produced by neuroendocrine cells, which are increased in the lungs of smokers. Bombesin-like peptides are chemotactic for monocytes, are mitogenic for epithelial cells and fibroblasts, and stimulate cytokine secretion (42). Tobacco glycoprotein, a constituent of tobacco, and other regulatory glycoprotein may also contribute to disease pathogenesis (12, 42).

DIP and RB-ILD show significant clinical, radiologic and histologic overlap, and in some patients the distinction is arbitrary and of uncertain clinical significance (10). In some individuals with PLCH, the extent of RB-ILD/DIP injury on lung biopsy may be very extensive, cause ground-glass attenuation on HRCT, and result in radiographic patterns that are suggestive of alternative diagnoses (9). Because RB-ILD and DIP are etiologically linked to smoking, it is not unexpected that RB/DIP-like reactions frequently coexist in histologic specimens from

patients with PLCH. However, only one recent study has described the extent and clinical significance of RB/DIP-like changes in patients with PLCH (9). The overlap between different radiologic findings of smoking-induced patterns of injury implies that caution is needed in establishing a diagnosis of these diseases without lung biopsy (9). Smoking cessation may prove to be the most important and effective therapeutic option for patients with "smoking-related ILD," and should be strongly encouraged. Pulmonary abnormalities can persist for long periods even after smoking cessation. It seems plausible that antigens in cigarette smoke or cigarette smoke–induced alterations in the lungs persist for long periods and may continue to provoke a chronic inflammatory reaction (22).

Future studies should investigate why some individuals are predisposed to develop smoking-related interstitial pneumonias, the relationship among these entities, prognostic factors, and therapeutic approaches for those patients who develop a progressive disease.

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