

Review Article

Smoking and Other Interstitial Lung Diseases

Carpio Carlos, Gómez-Carrera Luis, and Álvarez-Sala Rodolfo

Department of Pneumology, La Paz University Hospital, Paseo de la Castellana 261, 28046 Madrid, Spain

Correspondence should be addressed to Carpio Carlos, carlinjavier@hotmail.com

Received 12 May 2011; Accepted 3 June 2011

Academic Editors: K. Nishimura and M. Tatar

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Cigarette smoking has been implicated in the development of some uncommon respiratory interstitial diseases. Desquamative interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung diseases are characterized by a diffuse alveolar and peribronchiolar filling with macrophages, respectively. Pulmonary Langerhans' cell histiocytosis is a rare interstitial lung disorder characterized by the proliferation of Langerhans' cell forming interstitial infiltrates and nodules that could progress to cavitary nodules. The treatment of these disorders involves smoking cessation and sometimes the use of steroids. High-resolution computed tomography is essential for the characterization of these smoking-related interstitial lung diseases, but frequently it is necessary to create a workgroup composed by pulmonologists, pathologists, and radiologists to diagnosis and treat patients affected with these pathologies.

1. Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of nonneoplastic disorders resulting from damage to the lung parenchyma by varying patterns of inflammation and fibrosis. This group is characterized by dyspnea, diffuse parenchymal lung abnormalities, and restrictive pulmonary function [1].

Cigarette smoking and other forms of tobacco use represent the most preventable cause of premature morbidity and mortality in the United States [2]. Tobacco use is responsible for one in five deaths in the United States approximately and over 30% of all cancers are due to tobacco [3]. In addition, cigarette smoking is the principal risk factor for developing chronic obstructive pulmonary disease (COPD) and decline in the pulmonary function [3, 4].

Likewise, cigarette smoking has been related to the development of several ILDs, including desquamative interstitial pneumonitis (DIP), respiratory bronchiolitis associated ILD (RB-ILD), and pulmonary Langerhans' cell histiocytosis (PLCH). It is often used the term smoking-related interstitial lung diseases (SR-ILDs) to refer to them and to emphasize their relationship with the tobacco [1, 5–10]. In this paper, we describe and discuss possible pathogenetic mechanisms,

clinical features, radiologic findings, and outcomes of these SR-ILDs.

2. Relationship of Smoking with Interstitial Lung Disease

The relationship of smoking with DIP, RB-ILD, and PLCH has been supported by several clinical, epidemiological, and laboratory studies that had analyzed the role for cigarette smoking in the disease onset, progression, and recurrence of them. Respiratory bronchiolitis (RB), defined as the accumulation of pigmented macrophages in respiratory bronchioles and distal air channels, was first defined by Niewoehner et al. in 1974 [11]. Fraig et al. evaluated 156 surgical lung biopsies, and they found 109 cases of RB, corresponding 98% of cases to smoker patients. They also showed a persistence of the disease despite of quitting smoking. Likewise, the degree of cytoplasmic pigmentation was associated with the number of pack-years [12]. In the same way, Remy-Jardin et al., studied the parenchymal lesions of 41 smokers and they found the presence of pigmented macrophages in 69% of the patients [13]. In the study of Cottin et al. it was observed a diagnosis of RB in 88.6% of smoker patients who were

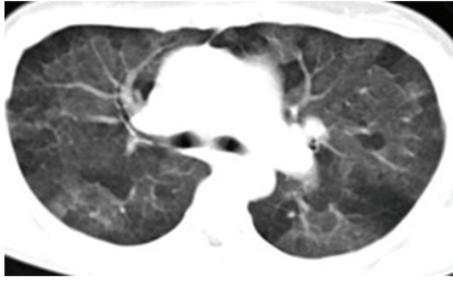


FIGURE 1: Desquamative interstitial pneumonia. High-resolution computed tomography showing areas of ground-glass attenuation.

operated for spontaneous pneumothorax [14]. Overall, the evidence suggests that RB occurs predominantly in patients who had a history of tobacco exposure, but smoking cessation is not always associated with RB regression [12].

In the case of RB-ILD, the link with cigarette smoking is also strong, since the clinical series showed that patients affected with RB-ILD were all smokers [15–17]. In DIP, it is known that most patients diagnosed with this disorder are smokers [17], however, this disease could also occur in nonsmokers people.

Cigarette smoking induces many inflammatory changes in the respiratory system and also enables the recruitment of macrophages, neutrophils, and Langerhans' cells [18, 19]. The peribronchial inflammation that occurs in RB-ILD, PLCH, and DIP could be secondary to the injury of small airways caused by the constituents of tobacco. In the same way, the macrophage accumulation that occurs in the airways and in the alveolar spaces is a key feature of the SR-ILDs. This macrophage accumulation also involves changes in the macrophage survival and in their apoptosis [20]. By the same way, the activation of epithelial cells, macrophages, and neutrophils indirectly promotes the generation of cytokines that lead to the increase of the inflammation [21].

3. Desquamative Interstitial Pneumonia

It was originally defined by Liebow et al. in 1965 [22]. Initially, it was believed that its histological feature was the desquamation of epithelial cells, but then it was recognized that the presence of intra-alveolar macrophages was due to an alveolar filling process [23]. This interstitial disorder is associated to tobacco in nearly 80–90% of patients [16, 17] but, in contrast to RB-ILD, this illness could also be associated to many drugs [24, 25], systemic disorders [26, 27], environmental exposures [28], and infections [29]. In addition, it also has been described in children [30].

The average age at the onset of symptoms is about 40 years, with a male predominance and a male-female ratio of 2:1 [1, 16, 17, 31, 32]. Clinical presentation of DIP is insidious and is characterized by progressive dyspnea and dry cough. Inspiratory crackles are present in 60% and digital clubbing in 50% of patients [1, 17]. Pulmonary function testing is characterized by a restrictive ventilatory defect and a decreased diffusion capacity [1, 32].

Bronchoalveolar lavage (BAL) cell analysis may show increased contents not only of macrophages but also of eosinophils [33]. Histologically, the main characteristic of DIP is the presence of pigmented macrophages within the alveolar spaces that stain in a nonspecific fashion with PAS-diastase [8]. Minimal to moderate alveolar septal widening usually accompanies the air-spaces changes but honeycombing is rare [16, 32]. Likewise, lymphoid aggregates may be present [1]. In RB-ILD, there also exists a macrophage accumulation, but it is accentuated within respiratory bronchioles and neighboring alveoli and is accompanied by a mildly thickening of the alveolar septa [15, 16]. The histological differential diagnosis includes illness characterized by intra-alveolar macrophage accumulation like usual interstitial pneumonia, RB, nonspecific interstitial pneumonia (NSIP), and eosinophilic pneumonia [1].

Radiologically, chest radiographs may be normal in 3–22% of biopsy-proven cases, but bibasal peripheral opacities have also been reported [1]. It is characterized finding in the high-resolution CT (HRCT), the presence of areas ground-glass attenuation [34] that is correlated histologically with the alveolar filling by macrophages [35] (Figure 1). DIP affects mainly peripheral lower lung areas [36]. Fibrosis may be present in 50–60% of the patients [34, 35], but honeycombing is rare [17]. On follow-up HRCT, patients receiving treatment can show partial or complete resolution of the areas of ground-glass opacification [37]. The CT differential diagnosis includes RB-ILD, NSIP, and acute hypersensitivity pneumonitis [34].

Smoking cessation must be considered very important to treat this disorder since there are reports of regression of the disease when patients stop smoking [38]. Patients with DIP are frequently treated with steroids observing stabilization or improvement of symptoms or pulmonary function in approximately two-thirds of patients [31]. Also, if left untreated, two-thirds of patients have evidence of clinical worsening. The 5- and 10-year-survival rates are 95% and 70%, respectively [31]. In the study of Ryu et al., it was observed that 60% of deaths were due to respiratory failure [17]. Also, recurrence in a transplanted lung has been reported [39]. Some authors have observed a possible progression of DIP to usual interstitial pneumonia, but there is little evidence yet [37].

4. Respiratory Bronchiolitis-Associated Interstitial Lung Disease

RB-ILD is the clinical manifestation of interstitial lung disease associated with the pathologic lesion of RB [1]. RB is a common incidental histologic finding occurring in the lungs of smokers, and it is manifested by the accumulation of macrophages within respiratory bronchioles [11, 40]. Most patients with RB are asymptomatic [11]. RB-ILD occurs when RB is associated with mild interstitial inflammatory changes and patients are usually symptomatic [15].

It has a slight male predominance [15, 16]. Usually, patients are 30 to 40 years old, and they have a history of more than 30 pack-years of cigarette smoking [7]. The usual

presenting symptoms are progressive dyspnea and cough [7, 41, 42]. These symptoms are usually mild, but in some patients the dyspnea could be significant and severe [1]. Finger clubbing is usually absent and inspiratory crackles could be present in one-half of patients [7, 16]. Pulmonary function testing may show restrictive, obstructive, or mixed abnormalities with reduced diffusing capacity [16, 42], and 11.5% have a positive bronchodilator response [42].

Radiologically, chest radiographs show frequently non-specific thickening of the central and peripheral bronchial walls. The chest radiograph is normal in 14% of patients [1, 17]. The HRCT findings most commonly include areas of ground-glass opacities, central, and peripheral wall thickening, and centrilobular nodules [42] (Figure 2). Upper lobe centrilobular emphysema could be associated [35] and honeycombing is rare [42]. The differential diagnosis includes acute hypersensitivity pneumonitis, DIP and NSIP [36].

Pathologically, it is characterized by the presence of pigmented macrophages within respiratory bronchioles and neighboring alveolar ducts and air spaces [15]. The brown and granular pigmentation of macrophages represents smoke constituents, most notably aluminum silicate [43]. Also, interstitial thickening accompanies the air-spaces changes but confined to the peribronchiolar parenchyma [32]. In the BAL, cellular analysis reveals an increased total numbers of cells with a normal cellular differential count [42]. Also, it contains alveolar macrophages with pigmented inclusions [44]. The histological differential diagnosis includes DIP, RB, and NSIP [1].

Patients with RB-ILD generally have a good prognosis. In the studies of Yousem et al. [16] and Myers et al., [15] all patients remained stable or improved during the follow-up period. Moreover, in the study of Ryu et al. [17], only 1 patient, who continued smoking, presented clinical worsening. A recent study, which had followed up 32 patients with diagnosis of RB-ILD during a mean of 84 months, observed only one death of progressive interstitial lung disease [42]. Smoking cessation had been reported as the principal treatment of RB-ILD [15–17], but in the study of Portnoy et al., subjective improvement was similar in patients who continued or discontinued smoking [42]. However, improvement of pulmonary function test was limited to the group that discontinued smoking [42]. Corticosteroids could be employed if disease progresses despite of successful smoking cessation [16], its role is controversial [42].

5. Pulmonary Langerhans' Cell Histiocytosis

The histiocytosis comprises a diverse group of proliferative disorders characterized by the infiltration and accumulation of histiocytes and other immune effector cells within various tissues. This initial classification system included Langerhans' histiocytosis (Class I), non-Langerhans' cell histiocytosis (Class II), and malignant histiocytosis (Class III) [45]. More recently, a revised classification schema included division into two groups: disorders of varied biological behavior and malignant disorders [46]. Each group is divided



FIGURE 2: Respiratory bronchiolitis-associated interstitial lung disease. High-resolution computed tomography showing central and peripheral wall thickening and areas of ground-glass opacities.

depending on the abnormal cell proliferation: dendritic cell or macrophages. PLCH is a rare granulomatous lung disease that is included in the dendritic cell abnormal proliferation subgroup of histiocytosis.

It represents less than 4% of all forms of ILDs [47] and is observed almost exclusively in smokers [48–51]. Cigarette smoking might predispose the accumulation of Langerhans' cell in the airways [19, 52] and also induces recruitment and activation of dendritic cells in bronchial and alveolar regions [53]. Cigarette smoking has also been associated with the presence of lung interstitial granulomas in PLCH [54]. Other cytokine abundant in PLCH patients is the transforming growth factor- β [55] and it has reported that cigarette smoke induces release of active TGF- β 1 [56].

The peak occurrence of PLCH is at 20–40 years of age with a male-female distribution almost equal [57–59] or with a slight male predominance [51]. Patients may present dyspnea, hemoptysis, and also systemic complaints like weight loss, fever, or fatigue [50, 51, 58, 59]. Up to one-quarter of patients may be asymptomatic [50]; however, respiratory complications like pneumothorax could appear in 15% of patients [50, 51, 58, 59]. Moreover, extrapulmonary manifestations like bone lesions, diabetes insipidus, and skin lesions are also described [50, 51, 58, 60]. Physical examination is often normal. On pulmonary function testing, restrictive, obstructive, and mixed patterns have been described and also reduction of the diffusing capacity [49–51, 58]. Exercise performance is often limited, and it is associated with the indices of vascular involvement [59].

Radiologically, chest radiograph is abnormal in most patients and reveals nodular or reticulonodular opacities most predominant in upper lung zones [51, 61]. HRCT findings are sensitive and specific for diagnosis of PLCH. The combination of nodules and cysts predominating in the upper and mid lungs are very suggestive of this disease. In early stages, it is frequent to observe nodules of different sizes with or without cavitation with a peribronchiolar distribution. In late stages, cystic changes appear in both lungs and become prominent [51, 57, 62]. Cysts may be irregular and more complex than those observed in pulmonary lymphangioleiomyomatosis. The lack of visible walls in emphysema may be the only discriminating feature [63]. The differential

diagnosis of nodules observed in HRCT includes sarcoidosis, silicosis, metastatic disease, and tuberculosis. Cystic disease should be distinguished from lymphangioliomyomatosis, emphysema, and idiopathic pulmonary fibrosis [36].

In the bronchoscopy, BAL cell analysis is helpful to the diagnosis when more than 5% of BAL cells stain with OKT6 antibodies [64, 65]. Histologically, nodules containing Langerhans' cells are present in early stages. They have a peribronchiolar distribution and also contain lymphocytes, macrophages and other inflammatory cells [66, 67]. Langerhans' cells are recognized immunohistochemically because they stain positive for CD1a and S100 [68] and at electron microscopy analysis they reveal intracytoplasmic Birbeck granules within them. Eosinophilic infiltration is often encountered in the early course of the disease [58]. With further progression, the infiltrate extends into the alveolar interstitium, with central fibrosis resulting in stellate lesions [69] and then, these infiltrates form necrotic nodules with cavitations [67]. In advanced disease, the lung contains areas of honeycombing and of paracicatricial emphysema more predominantly in the upper lobes [58, 67].

Smoking cessation is recommended, since it has been associated with stabilization of symptoms and radiological improvement [70–72]. Also, systemic pharmacotherapy is considered when patients continue to get worse despite smoking cessation. Corticosteroids could be used but their efficacy is unclear [51, 57, 58]. Other immunosuppressive agents like vinblastine, cladribine, cyclophosphamide, and methotrexate have been used to treat progressive PLCH, but their utility is not well-defined [57, 73–75]. Progression of the disease to pulmonary fibrosis and death are uncommon, and survival is associated with the diffusing capacity, pulmonary function testing, smoking status [49, 50] and the occurrence of pneumothorax [51]. In cases where the clinical status worsens and treatment is ineffective, lung transplantation is indicated, but it has been described the recurrence of the disease after lung transplantation [76].

6. Conclusions

According to the World Health Organization, tobacco use is the second major cause of death in the world [2]. Cigarette smoking has an important role in the pathogenesis of certain ILDs like DIP, RB-ILD, and PLCH. The high prevalence of tobacco smoking could increase the prevalence of these SR-ILDs globally in the next years. These disorders usually have an insidious onset and a good prognosis. It is important to always utilize smoking cessation therapies for patients affected by these diseases because it may improve or stabilize symptomatology and radiological involvement.

Contributions of the Authors

This paper is signed by 3 authors. All the authors have drafted and amended the paper and approved the final version.

Conflict of interests

No conflict of interests indicated by the authors.

Abbreviations

ILDs:	Interstitial lung diseases
SR-ILDs:	Smoking-related interstitial lung diseases
COPD:	Chronic obstructive pulmonary disease
DIP:	Desquamative interstitial pneumonitis
RB-ILD:	Respiratory bronchiolitis-associated interstitial lung disease
PLCH:	Pulmonary Langerhans' cell histiocytosis
BAL:	Bronchoalveolar lavage
NSIP:	Nonspecific interstitial pneumonia.

Disclosure

Role of sponsors: No commercial sponsor had any involvement in the design and preparation, decision to submit, review, or approval of the paper.

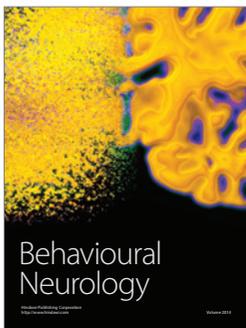
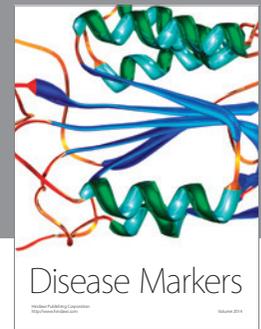
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