



REVIEW

An integrated approach in the diagnosis of smoking-related interstitial lung diseases

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ABSTRACT: Cigarette smoke consists of several chemical compounds with a variety of effects in many organs. In the lung, apart being the main cause of chronic obstructive pulmonary disease, carcinoma and idiopathic spontaneous pneumothorax, tobacco smoke is associated with interstitial lung diseases (ILDs), including respiratory bronchiolitis-associated ILD (RB-ILD), desquamative interstitial pneumonia (DIP), pulmonary Langerhans' cell histiocytosis (PLCH), idiopathic pulmonary fibrosis, acute eosinophilic pneumonia, ILD in rheumatoid arthritis and pulmonary haemorrhage in Goodpasture syndrome.

This review will focus on the diseases with a stronger epidemiological association with tobacco smoke, namely RB-ILD, DIP and PLCH. Although the exact pathogenetic evidence linking smoking with these disorders is still not completely understood, there is growing evidence that tobacco smoke targets the terminal or respiratory bronchioles in these diseases, and the differences are reflective of the degree of severity of small airway and parenchymal reaction to the smoke exposure.

Despite considerable clinical, radiological and histological overlap between RB-ILD, DIP and PLCH, it is useful to retain the separate classifications for prognostic and therapeutic implications.

KEYWORDS: Desquamative interstitial pneumonia, interstitial lung diseases, Langerhans' cell histiocytosis, respiratory bronchiolitis, smoking

The influence of tobacco smoke on human health is still an important problem in the developed world. Complex inflammatory processes and changes in the immune system are crucial in the pathogenesis of smoking-related disorders, such as chronic obstructive pulmonary disease (COPD), emphysema, lung cancer and atherosclerosis. The term asymptomatic smoker implies a healthy smoker, *i.e.* without clinical symptoms of chronic bronchitis and with normal values of pulmonary function tests, which is differentiated from a smoker with signs of COPD or interstitial diseases. However, the line of division is difficult to define because of the possibility of asymptomatic bronchiolitis [1]. The role of tobacco smoke in the pathological processes of small airways is well documented [2, 3]. The cause–effect relationship between a history of cigarette smoking and interstitial diseases is a more recent acquisition. Respiratory bronchiolitis (RB) is present pathologically in most smokers, but

very few of them experience symptoms. RB is characterised by airway-centred accumulations of macrophages containing fine, granular yellow-brown cytoplasmic pigments (“smoker’s macrophages”) within distal bronchioles, alveolar ducts and adjacent alveolar spaces. Cytoplasmic pigmentation is variable and correlates with the numbers of pack years smoked [4]. RB represents a highly specific physiological response to smoking. RB-associated interstitial lung disease (ILD) is the term used to describe smokers who become symptomatic secondary to RB [5]. RB-ILD is an uncommon ILD that occurs in a small proportion of smokers [5]. Because of the significant overlap in clinical, radiological and histological features between RB-ILD and desquamative interstitial pneumonia (DIP), these entities are considered a pathomorphologic continuum, representing different degrees of severity of the same disease process [6–10]. However, there are prognostic reasons for continuing to separate RB-ILD from

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DIP when possible. The mortality of patients with DIP is 6–30%, while only rarely have patients with RB-ILD been reported to die of their disease [5, 11–15]. Additionally, patients with DIP may develop acute exacerbations [16–18]. DIP is one of the rarest idiopathic interstitial pneumonias and is characterised by the diffuse accumulation of large numbers of pigmented macrophages in alveolar spaces associated with interstitial inflammation and/or fibrosis [19]. In the majority of cases, DIP is considered to be a smoking or dust inhalation-related interstitial pneumonia. The association of organ-specific immunological diseases and elevated antinuclear antibody, observed in some cases, and bronchoalveolar lavage (BAL) eosinophilia/neutrophilia in DIP suggest that the pathogenesis may be immunologically mediated [13, 20]. Pulmonary Langerhans' cell histiocytosis (PLCH) is a non-neoplastic reactive process to cigarette smoke. It is characterised by multiple stellate cellular nodules centred around, or adjacent to, small airways. Over time, these lesions show increasing amounts of stellate fibrosis with cyst formation [21, 22]. The cystic cavities represent the highly distorted bronchiolar lumen resulting from the destruction of the airway walls by Langerhans' cell (LC) granuloma [23]. The relationship of smoking with RB-ILD, DIP and PLCH has been largely established on the basis of epidemiological evidence. These diseases are correctly considered as distinct and separate conditions in the classification of ILDs, but these three entities share a number of clinical, radiological and pathological features, suggesting that they represent a spectrum of patterns of ILDs occurring in predisposed individuals who smoke. The association of pulmonary emphysema with non-specific interstitial pneumonia (NSIP) provides support for cigarette smoking as a pathogenetic factor in a subset of NSIP patients in recent studies [24–27]. Acute eosinophilic pneumonia is a dramatic response to recent onset smoking in a small number of individuals [28]. Recently, a new entity has been highlighted, combined pulmonary fibrosis and emphysema (CPFE) [29]. Not just a distinct phenotype of idiopathic pulmonary fibrosis (IPF), the syndrome of CPFE is characterised by the association of distinct features, including: tobacco smoking; severe dyspnoea; unexpected near normal lung volumes; severely impaired diffusing capacity of the lung for carbon monoxide (DL_{CO}); hypoxaemia at exercise; characteristic radiological features (centrilobular and/or paraseptal emphysema, and diffuse interstitial aspects suggestive of pulmonary fibrosis at the lower lobes); frequent association with pulmonary hypertension; and poor prognosis [30–32]. This review will focus on the diseases with a stronger epidemiological association with smoke, namely RB-ILD, DIP and PLCH.

HISTOLOGICAL–RADIOLOGICAL CORRELATIONS

RB and other abnormalities

From the pathologist's perspective, the most characteristic effect of tobacco smoke on lung parenchyma is RB, consisting of the presence of bronchioles and peribronchiolar alveoli of finely pigmented, iron-containing (smoker's) macrophages in the lumen (fig. 1a) [4, 33, 34]. The degree of pigmentation is related to the number of pack-years smoked [4]. In heavy smokers, particularly marijuana smokers [35], the pigment can become coarser and the distinction with haemosiderin due to chronic haemorrhage may be difficult to identify on purely histological grounds, therefore, clinical evidence is required. The changes are patchy at low magnification, generally with a striking bronchiolocentric distribution (fig. 1b); however,

smoker's macrophages may variably extend to the peripheral alveoli, occasionally involving the entire lobule (fig. 1c). The amount of pigmented macrophage accumulation within respiratory bronchioles observed histologically correlates with the profusion of centrilobular nodules on high-resolution computed tomography (HRCT) [36]. Such nodules are poorly defined and separated from the pleural surfaces, fissures and interlobular septa by several millimetres (fig. 1d) [37]. The intensity of macrophage accumulation in the alveoli and alveolar ducts is linked to the extent of ground-glass attenuation on HRCT [36]. However, ground-glass opacities do not exclusively correspond to macrophage accumulation at histology as they may also be caused by mild interstitial inflammation and/or fibrosis [36].

Frequently, smoker's macrophages are associated with subtle histological features of chronic bronchiolitis, including mild lymphocytic inflammation and mild fibrosis of the bronchiolar wall and surrounding alveolar septa; sometimes with rigidity and distortion of the bronchiolar lumen, bronchiolectasia and mucostasis. Although these changes can be prominent enough to be histologically indistinguishable from constrictive bronchiolitis, they generally only have minor clinical consequences in the form of mild airflow obstruction. It is conceivable assuming that scattered lobules of reduced attenuation on HRCT, confirmed as lobular air trapping on expiratory computed tomography scanning, may be correlated with the remodelling of both membranous and respiratory bronchioli. However, air trapping is not as extensive on HRCT as is observed in other mixed interstitial and small airways diseases [38]. Air trapping may be accompanied by a slight thickening of the larger (*e.g.* subsegmental) intralobar airways, possibly reflecting changes of chronic bronchitis [39].

RB is very frequent in smokers, and probably is the most sensitive and specific histological marker of tobacco smoke. In a study on 156 surgical specimens [4], RB was found in all 83 current smokers and in only two out of 24 never-smokers; however, the smoking history was controversial in both groups. Interestingly, RB was also present in ~50% of ex-smokers, sometimes persisting many years after smoking cessation. Of the 109 patients who had RB, RB was the cause of an ILD in only two (RB-ILD and DIP in one patient each). In other words, RB is generally a histologically incidental finding in smokers (as the biopsy is obtained for another reason, for example, a carcinoma), and only rarely does RB cause an ILD. Although patients with ILDs have, in general, more severe histological alterations, histology alone is unable to predict the presence of ILD in a single case. Similarly, RB and RB-ILD cannot be distinguished solely from the nature of HRCT abnormalities, as there is no arbitrary cut-off in HRCT disease extent at which RB becomes RB-ILD. However, the extent of disease on HRCT images should be taken into account when reaching the decision that clinically significant ILD (*i.e.* RB-ILD) is present [40]. The distinction between RB and RB-ILD varies greatly in the literature. Recently, CHURG *et al.* [41] proposed a strict definition of RB-ILD, which we concur with; therefore, following this definition, RB-ILD should be restricted to smokers with restrictive or mixed obstructive and restrictive functional abnormalities, with a marked decrease in diffusing capacity with minimal airflow obstruction, or with ground-glass opacities/centrilobular nodules plus reticulation at HRCT, and no other lesions besides RB on biopsy.

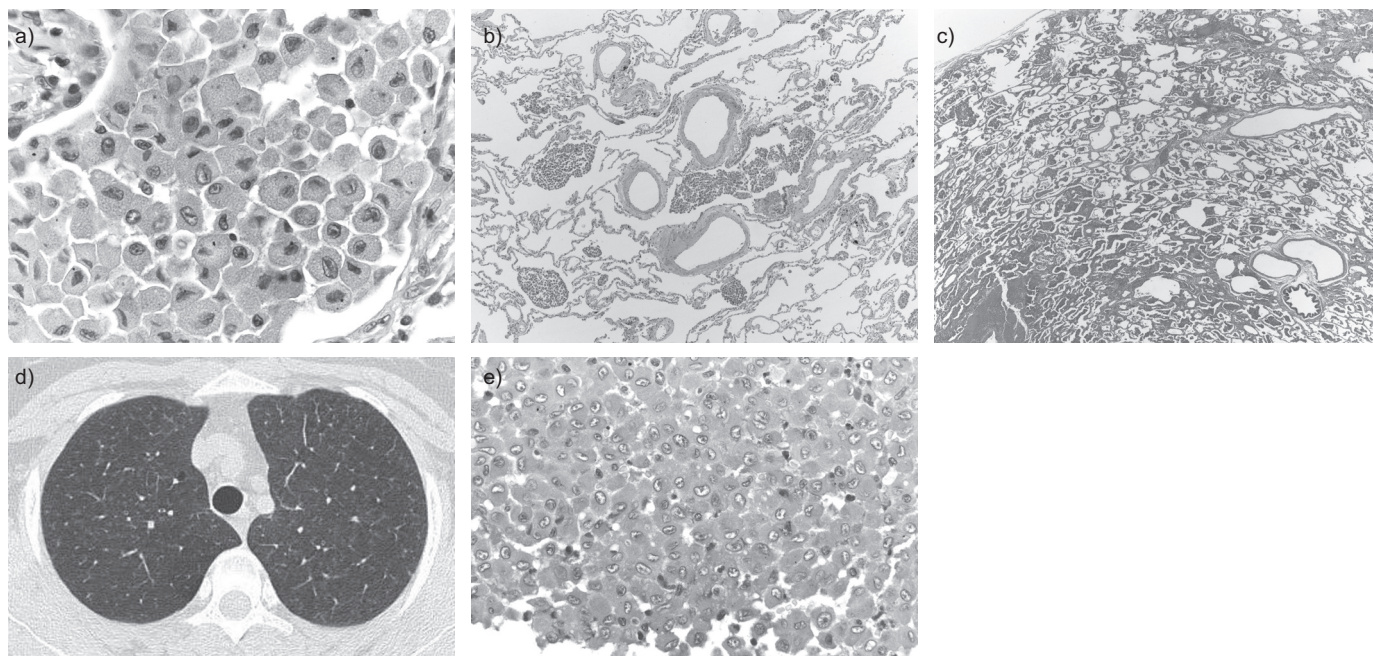


FIGURE 1. a) Respiratory bronchiolitis: the intra-alveolar accumulation of finely pigmented macrophages (smoker's macrophages) (haematoxylin and eosin, 400 ×). Generally smoker's macrophages have a strict bronchiolocentric distribution (b; haematoxylin and eosin 40 ×), but occasionally they involve the entire lobule (c; haematoxylin and eosin, 20 ×). d) Respiratory bronchiolitis in a 63-yr-old heavy smoker who was asymptomatic at the time of computed tomography. The high-resolution computed tomography image shows bilateral poorly defined centrilobular nodules in the upper lobes. e) Occasionally, particularly in desquamative interstitial pneumonia, a relatively large number of eosinophils are present and the limits with chronic eosinophilic pneumonia are sometimes blurred (haematoxylin and eosin, 200 ×).

Once the clinician has established the presence of an ILD due to RB, the distinction between RB-ILD and DIP is mostly based on the extension of smoker's macrophages: in RB-ILD the latter are restricted to the centrilobular area, whereas in DIP they involve the lobule more diffusely. Moreover, interstitial fibrosis (see below), lymphoid follicles, giant cells and eosinophils are more frequent in DIP than RB-ILD [13, 18]. In some patients with DIP the number of eosinophils (both in tissue and BAL) is high enough to raise concern about the possibility of chronic eosinophilic pneumonia (fig. 1e). However, the limits between RB-ILD and DIP are blurred and in practice the distinction can be difficult and, in some cases, is probably quite arbitrary; depending on sampling, the degree of alveolar filling from smoker's macrophages can vary from one lobule to another. Due to this, some authors suggest that RB-ILD and DIP should be grouped into one category [10]. However, we share the opinion of the majority that they should be classified separately whenever possible because of the differences in clinical presentation and prognosis, acknowledging that in rare cases the distinction is impossible [40]. On HRCT, RB-ILD differs from DIP in that ground-glass attenuation of RB-ILD is usually less extensive, more patchy and more poorly defined. A peripheral, sub-pleural and basal predominance of ground-glass opacity reflecting either accumulation of intra-alveolar macrophages or septal thickening is most commonly seen in DIP [7]. Although HRCT features can be useful in identifying probable DIP rather than RB-ILD, the overlapping features on HRCT scans in some cases and the occasional histological coexistence of the two entities further emphasise the need for an integrated clinical, radiological and pathological approach to secure a correct diagnosis [42].

Fibrosis and emphysema

The tendency for cigarette smokers to develop limited or extensive interstitial fibrosis is increasingly being reported by radiological and histological studies. In an accurate histological study on surgical resections performed for lung cancer, KAWABATA *et al.* [43] found foci of fibrosis with usual interstitial pneumonia (UIP) pattern in the non-neoplastic lung in 21.3% of smokers (125 out of 587), frequently without overt clinical features of ILD (only 49 patients had a pre-operative clinical diagnosis of IPF). No long-term follow-up was provided so the significance of this finding is unknown but, interestingly, all the patients who developed acute respiratory failure following surgery had UIP foci at histology. It is worth noting that, in a very different clinical setting (surgical biopsy performed because of ILD), the histological diagnosis of early UIP arising in the background of chronic smoking-related abnormalities is occasionally difficult.

A recent study by WASHKO *et al.* [44], showed that ~5% of a large cohort of smokers (41% met the criteria for COPD) displayed minimal sub-pleural interstitial abnormalities on HRCT. However, extensive interstitial abnormalities were found in only 0.8% of the study population [44]. Another recent study showed that the prevalence of extensive interstitial abnormalities among HRCT examinations of smokers recruited by a lung cancer screening trial was 4%, with a UIP-like pattern and NSIP-like pattern reported in 0.3 and 3.7% of the cases, respectively. Intriguingly, the interstitial abnormalities increased in extent among persistent current smokers, whereas they decreased in quitters [45]. In both studies, smokers with sub-pleural changes were more likely than those

without these abnormalities to be older. An intriguing possibility is that the lung abnormalities related to cigarette smoking are analogous to those seen in elderly nonsmokers, suggesting that cigarette smoking may have a premature ageing effect on the lungs [38, 46]. Indirect evidence for the idea of the development of fibrotic elements as part of the ageing process has come from a study by COPLEY *et al.* [46], in which a basal sub-pleural reticular pattern was identified in 60% of HRCTs of healthy individuals aged >75 yrs but in none of those aged <55 yrs [46].

Although emphysema is classically defined as permanent airspace enlargement without “obvious” (macroscopic) fibrosis [47, 48], in reality some microscopic fibrosis is quite frequent in centrilobular and, particularly paraseptal emphysema, and often quite prominent [49, 50]. KATZENSTEIN *et al.* [51] identified fibrosis involving >25% of slides in 20 (60%) extensively sampled lobectomy specimens from smokers. Importantly, the authors noted that fibrosis, although sometimes histologically quite dramatic, did not produce clear clinical abnormalities, being an incidental finding in smokers undergoing operations for other reasons. Reported in the literature with terms (RB-ILD with fibrosis [24], airspace enlargement with fibrosis [43], smoking-related interstitial fibrosis [51]), fibrosis in this setting has a typical dense, amyloid-like character and is more prominent in sub-pleural and peribronchiolar parenchyma, where it frequently surrounds emphysematous spaces (fig. 2a and b). Sometimes large emphysematous holes are criss-crossed by bands of fibrosis. Fibrosis that is not associated with emphysema can also occur.

Limited fibrosis combined with pulmonary emphysema may be too fine to be seen on HRCT images. However, mild ground-glass opacification and fine intralobular reticulation may be observed in confined emphysematous areas on HRCT images (fig. 2c). Future investigations are needed to assess this type of HRCT pattern. Nonetheless, it has been shown that diffuse fibrosing interstitial pneumonia, most commonly UIP, occurs in patients with emphysema. COTTIN *et al.* [30] have proposed that such cases fall under the subheading of CPFE, which may have distinctive clinical implications (*e.g.* increased incidence of pulmonary hypertension as compared to similar forms without emphysema). Differentiation of NSIP from UIP by HRCT becomes more difficult in cigarette smokers with emphysema. In a study of 54 patients with NSIP and 42 patients with UIP, the

computed tomography diagnosis was correct in 44% of readings in those with concurrent emphysema, compared with 68% in those without concurrent emphysema [52].

In some smokers with ILD, fibrosis is so prominent that it makes the differential diagnosis between DIP and fibrotic NSIP difficult, both histologically and radiologically. Moreover, some authors suggest that DIP can evolve into NSIP [8], and that some cases of fibrotic NSIP can be related to tobacco smoke. In a retrospective HRCT study, MARTEN *et al.* [26] compared the prevalence and extent of emphysema in smokers with NSIP *versus* smokers with COPD and “healthy” smokers. The authors reported emphysema in a striking majority of NSIP cases (77.8%) and COPD cases (73.5%) but not so in the “healthy” smokers (17.5%). The high prevalence of emphysema in the NSIP patients, which did not differ from the COPD controls, provided indirect support for a smoking pathogenetic hypothesis in some NSIP patients. Although compelling, these hypotheses are as yet unproven. In our practice we try to separate DIP and fibrotic NSIP whenever possible, particularly because the prognosis of DIP appears to be better than fibrotic NSIP, again acknowledging that, in occasional cases, the distinction is difficult and probably arbitrary.

Increase in LCs

Another common effect of smoking is the increase in the number of LCs, which are detectable in lung tissue and BAL. LCs are characteristic both on morphology (moderate amount of pale cytoplasm, deeply infolded nuclei) and immunophenotype (positivity for S-100 protein, CD1a and Langerin [53]). By definition, in PLCH LCs form clusters, but the limits between PLCH and a simple increase in LCs in a smoker are conventional and sometimes blurred. PLCH occurs when LCs accumulate in the bronchiolar wall (fig. 3a) and disperse into the surrounding alveolar septa, forming multiple stellate nodules centred on small airways (fig. 3b) [54, 55]. On HRCT, nodules are usually <5 mm in diameter, and have a peribronchiolar and centrilobular distribution. The extent of nodular lesions on HRCT is strongly correlated with the density of lesions in the bioptic specimens [56].

Together with LCs, these cellular nodules frequently incorporate a variable number of eosinophils and smoker’s macrophages, both in surrounding alveolar spaces and in the interstitium. An associated RB is almost universal and sometimes extensive,

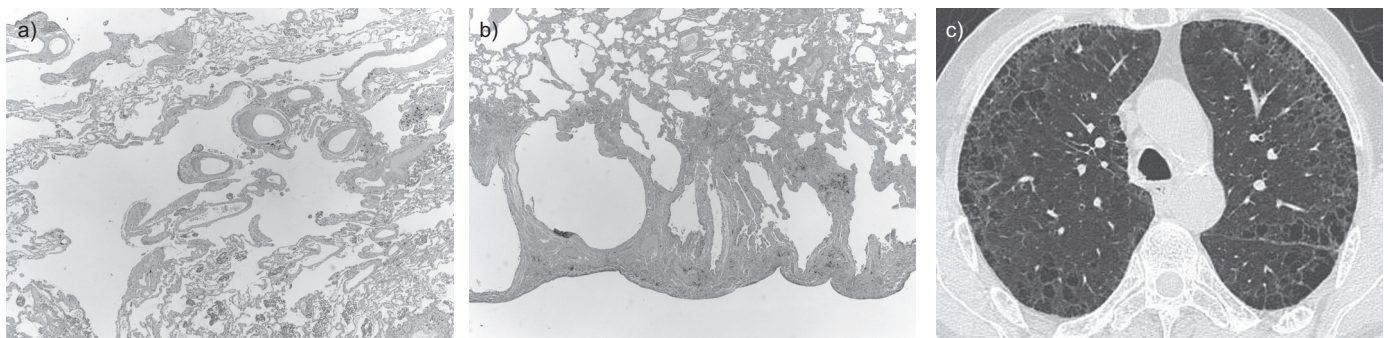


FIGURE 2. Smoking-related fibrosis with dense acellular fibrosis that frequently surrounds cystic emphysematous spaces, both in a) centrilobular (haematoxylin and eosin, 40 ×) and b) sub-pleural parenchyma (haematoxylin and eosin, 20 ×). c) Specific smoking-related interstitial abnormalities in a heavy smoker with dyspnoea. A high-resolution computed tomography image showing mild ground-glass opacity and reticulation circumscribing emphysematous areas.

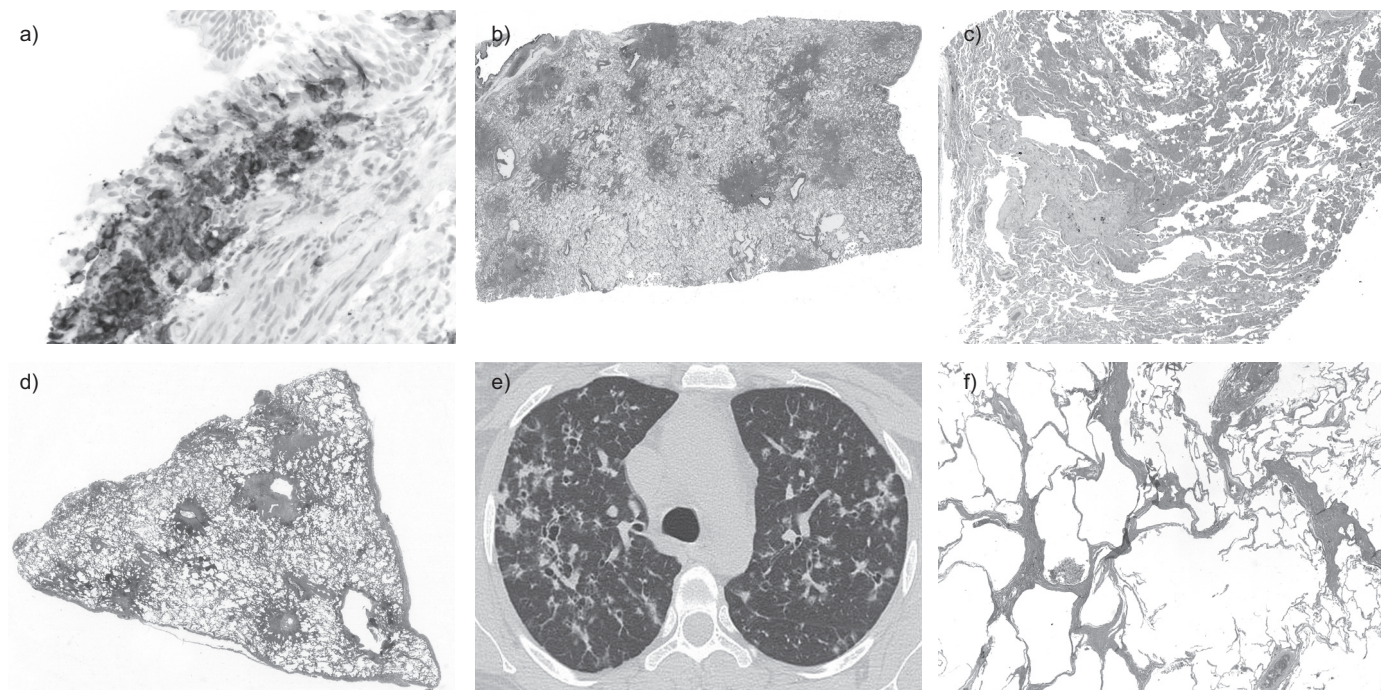


FIGURE 3. a) Pulmonary Langerhans' cell histiocytosis (PLCH) is characterised by an increased number of CD1a+ Langerhans' cells in the bronchiolar wall (200 ×). b) In the early/active phase of PLCH stellate cellular nodules with a bronchiolocentric distribution can be seen (haematoxylin and eosin, 10 ×). c) A stellate fibrotic nodule suggestive of healed PLCH is present on the left and is associated with an extensive accumulation of smoker's macrophages (haematoxylin and eosin, 20 ×). d) Classical example of PLCH in its mature phase consisting of multiple bronchiolocentric cellular nodules, some of which are fibrotic and irregularly cavitated (haematoxylin and eosin, 10 ×). e) A high-resolution computed tomography image at the level of the upper lobes showing numerous irregularly margined bilateral nodules; a few cysts are visible. f) Chronic PLCH showing stellate scars with paracicatricial emphysema (haematoxylin and eosin, 40 ×).

being visible on computed tomography scans as ground-glass opacities (fig. 3c) [42]. Over time, the centre of the nodules becomes fibrotic and irregular cavities develop in some of the nodules, leading to the classical histological features of mature PLCH, multiple stellate nodules, some of which are cavitated and surrounded by normal lung (fig. 3d). HRCT images closely mirror the pathologic findings, showing some of the nodules that cavitate. In more advanced stages, the HRCT appearance is characterised by a cystic-nodular pattern mostly involving the upper lobes, which usually permits a confident diagnosis (fig. 3e). Nodules and cysts can occur independently of each other, but in the majority of patients they are found concomitantly. However, end-stage PLCH, when the distribution characteristics are less obvious, may be difficult to distinguish radiologically from other cystic lung diseases, such as lymphangiomyomatosis (in females), lymphocytic interstitial pneumonia and, above all, emphysema [57].

The outcome of these lesions varies from case to case, probably depending on the abstinence from smoking and from individual predisposition. In many cases the nodules reabsorb completely or form small bronchiolocentric scars with paracicatricial emphysema (fig. 3f). It is reasonable to assume that some cases of centrilobular emphysema with fibrosis are in reality examples of healed PLCH. Recent observations show that even cystic lesions in PLCH, as observed on HRCT, harbour active granulomas on histopathology regardless of their wall thickness, and may show improvement on serial computed tomography controls [58]. In a minority of patients progressive fibrosis develops;

the stellate shape of the scars, their bronchiolocentric distribution with a prevalence in the upper lobes, and the absence/paucity of fibroblastic foci are characteristic of chronic PLCH and are sufficient for a firm diagnosis in the majority of the cases, even in the absence of residual LCs. Occasionally, however, the histological differential diagnosis with UIP is difficult and requires a strict correlation with clinical–radiological findings. As for RB, emphysema and fibrosis, PLCH can also be a histological incidental finding in the lung specimen removed for another disease, for example carcinoma.

Summary of histological and radiological findings

As we have seen, tobacco smoke can cause many histological and radiological abnormalities (table 1). These abnormalities can be variably combined, creating a significant overlap among the different entities. Moreover, they frequently provide a backdrop for other diseases that are more clinically relevant. For these reasons, in order to establish the significance of histological and radiological findings a close correlation with clinical data is mandatory.

Clinical and functional aspects in RB-ILD and DIP

Patients with RB-ILD or DIP are usually 30–40 yrs of age and have an average smoking history of 30 pack-yrs [7, 11]; males are affected approximately twice as often as females [59, 60]. Symptoms and clinical aspects in both these diseases are non-specific. Slowly progressive exertional dyspnoea and cough (which may be not productive) are the most frequent symptoms of presentation [5, 6, 11, 40]. The presence of symptoms, mainly

TABLE 1 Main histological lesions due to smoking and corresponding high-resolution computed tomography (HRCT) findings

Histology	HRCT
Smoker's macrophages within bronchiolar lumens and surrounding alveolar spaces, mild bronchiolar fibrosis and inflammation	Hazy centrilobular nodules Patchy ground-glass opacity
Mild distortion of bronchiolar lumens with bronchioloectasia and mucostasis	Mild bronchial dilatation with wall thickening; mild air-trapping at expiratory computed tomography scanning
Centrilobular and subpleural emphysema	Centrilobular and paraseptal emphysema
Dense interstitial fibrosis, frequently surrounding emphysematous holes	Peripheral and intralobular reticulation, ground-glass opacity intermingled with emphysematous areas
Increase in Langerhans' cells forming stellate bronchiolocentric nodules, some of which are irregularly cavitated and fibrotic	Ill-defined or cavitated centrilobular nodules

in RB-ILD, is not consistent; the disease may be diagnosed in asymptomatic patients with functional impairment, end-inspiratory crackles on pulmonary examination and chest radiograph or HRCT abnormalities [40]. Bilateral basal inspiratory crackles are frequent (~50–60% of DIP cases, rarer in RB-ILD), whereas clubbing is rare [6].

Despite the bronchiolocentric nature of disease in RB-ILD, both restrictive and obstructive alterations have been described [5, 6], with a mixed, predominantly restrictive, ventilator defect, usually associated with a mild-to-moderate reduction in DL_{CO} , the most frequent finding [5, 6]. There is no complete correspondence between histological and functional severity of disease; some patients with near normal pulmonary functional evaluation have moderately extensive fibrotic change radiating from the bronchioles at lung biopsy [4]. However, this is likely to reflect the problem of sampling error [40, 61], with histological severity at biopsy not representative of the severity of the lung involvement. In DIP, the functional abnormality is predominantly restrictive with the DL_{CO} reduction a useful guide to the underlying severity of the disease. An important confounder in the interpretation of functional impairment in both RB-ILD and DIP is the frequent concomitant presence of emphysema. In these cases, the presence of emphysema may justify a predominantly obstructive defect on pulmonary function tests. A mild obstructive alteration may be due to concomitant chronic bronchiolitis. In other cases the co-existence of emphysema and fibrotic changes may give rise to paradoxically normal lung volumes associated with a disproportionate reduction in DL_{CO} [5, 6].

Clinical and functional aspects in PLCH

PLCH is a rare disease [62]. The classification of histiocytic disorders has been simplified and is based on the presence of single or multi-organ involvement [63]. In the latter case, lung disease is most commonly found in children and is not associated with smoking. The significant clinical and epidemiological differences between the pulmonary and systemic forms of the disease suggest that although the pivotal cell may be the same (LC), the pathogenetic pathways are different [63–67]. More than 90% of patients with isolated PLCH are current or former smokers [63–67]. Although the proposed pathogenesis of PLCH revolves around an immune response involving locally recruited LCs and other inflammatory/immune cells, the trigger for cellular proliferation appears to be an inhaled

antigen, probably residing in tobacco smoke [67, 68]. This hypothesis is supported by the peribronchiolar distribution of the lesions in this disease. LCs are differentiated antigen-presenting cells of monocyte-macrophage lineage occurring in the normal lung [63]. The origin of the expanded population of LCs in the lungs is unknown. The increase of LCs may be due to local proliferation of the cells but a more important mechanism is considered to be accumulation, through enhanced recruitment of circulating precursors and delayed apoptosis [69–72]. Recently, a report demonstrated that 50% of patients with LC histiocytosis have a somatic mutation of the oncogene BRAF, V600E. This observation strongly suggests that LC histiocytosis is a neoplastic disease [73]. The presence of BRAF V600E in PLCH was surprising considering the fact that 70% of pulmonary diseases have been reported to be polyclonal; the significance of this observation is not well understood. PLCH probably represents a polyclonal reaction to cigarette smoking in predisposed individuals [74]. Not surprising, many patients with PLCH frequently show RB/DIP-like reactions in lung biopsies. The disease affects young adults between 20 and 40 yrs of age. No clear sex predominance of the disease has been described. Patient's presentation consists of dyspnoea, dry cough and chest pain, as well as constitutional symptoms (fever, malaise and weight loss) but the disease may be asymptomatic (in ~25% of patients) [63, 65]. In the latter case, abnormal chest radiographs are the only alterations and chest radiography is performed for other reasons. Haemoptysis is an unusual symptom in PLCH and should lead to investigations for an alternative diagnosis or superimposed lung carcinoma in these smoking patients. Measures of DL_{CO} are more sensitive in detecting lung involvement than lung volumes measurements, which could show normal, obstructive, restrictive or mixed patterns [60, 75, 76]. A recent study shows that airway obstruction was the prevalent pattern of lung function defect observed at diagnosis and during follow-up [77]. Cystic bone lesions may be identified in ~10% of patients and may precede the development of lung disease [60]. Diabetes insipidus and skin lesions may be present [63]. Pneumothorax with chest pain is the initial clinical presentation in 15% of patients with PLCH and may be recurrent, requiring chest tube placement and thoracotomy [78]. Pleurodesis is often required because of the high rate of recurrence. Physical examination is usually indifferent except in cases of pneumothorax. Pulmonary hypertension is more prominent in advanced PLCH than in other

chronic lung diseases owing to direct intrinsic pulmonary vascular/vasculitic involvement [79, 80]. PLCH has been described in association with lung cancer as well as extra-pulmonary cancers and lymphoma, especially Hodgkin disease [67, 81, 82]. Neoplasms may be either synchronous with PLCH, precede it or appear at another time. The occurrence of lung cancer and other tobacco smoke-associated malignancies probably reflects the impact of smoking as a common aetiological agent for each disease [67]. Prior treatment with chemotherapeutic agents and chromosomal or genetic abnormalities are factors that may confer a predisposition to the development of malignant neoplasms in patients with PLCH. Clinical and functional aspects of RB-ILD, DIP and PLCH in comparison with CPFE are shown in table 2.

The role of BAL

BAL examination represents an important step in the diagnosis of ILD [83]. In the majority of cases, the results of BAL fluid examination only provide additional information and cannot be used as the basis for definitive diagnosis of ILD. However, this relatively noninvasive procedure is very useful in the differential diagnosis of ILD; the normal cellular count of BAL excludes active inflammation. The typical pathological features in smoking-related ILD, RB-ILD and DIP is an important and significant increase in total cells counts and in the number of pigmented alveolar macrophages. The frequent observation in

DIP is an increase in the percentage of eosinophils and neutrophils. The BAL findings are not specific or diagnostic.

In PLCH the finding of >5% of LCs in BAL strongly suggests the diagnosis in the appropriate clinical–radiological setting. This cut-off distinguishes between patients with PLCH and smokers without PLCH and other ILDs but reduces the test sensibility [84, 85]. In our series of 27 patients with a diagnosis of PLCH, bronchoscopic evaluation with BAL was performed in 16 patients and BAL was diagnostic in four (25%) cases (unpublished data). Our results are in agreement with data in which a BAL sensitivity of <25% is reported in PLCH diagnosis. In PLCH, a macrophagic alveolitis that reflects the smoking history of the patients is typically present.

DIAGNOSTIC WORK-UP OF PATIENTS WITH SUSPECTED SMOKING-RELATED ILDS

Diagnosis of RB-ILD and DIP

The diagnosis of RB-ILD is essentially a clinical-functional-radiological-histological diagnosis and is based on global markers of disease severity (symptoms, pulmonary functional impairment and HRCT abnormalities), not on histological evaluation in isolation. RB-ILD is histologically indistinguishable from RB and RB is a very common, and possibly incidental, finding in cigarette smokers. The discovery of RB on lung biopsy is not equivalent to a diagnosis of RB-ILD. Since the clinical features of RB-ILD may be confused with other ILDs and the imaging

TABLE 2 Clinical features of respiratory bronchiolitis-interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP) and pulmonary Langerhans' cell histiocytosis (PLCH) in comparison with combined pulmonary fibrosis and emphysema (CPFE)

	RB-ILD	DIP	PLCH	CPFE
Smoking	100%	90%	>90%	100% (heavy smokers)
Age	3rd to 5th decade	3rd to 5th decade	3rd to 4th decade	6th to 7th decade
Sex M:F	Slight male dominance	Nearly 2:1	1:1	Almost all male
Onset	Insidious	Insidious	Insidious	Insidious
Presenting symptoms	Dyspnoea and cough	Dyspnoea and cough	Dyspnoea, cough and acute chest pain (when pneumothorax is present)	Dyspnoea and cough
Systemic involvement	No	Possible, rare	Possible	No
Crackles	~50%	60%	Usually absent	87% basal
Clubbing	Rare	Nearly 50%	Exceptional	43%
Pulmonary function	Mixed defect or normal; reduced DLCO	Restrictive; reduced DLCO	Obstructive or restrictive; reduced DLCO (especially in patients with vascular involvement)	Sub-normal pulmonary volumes; severe reduction of DLCO
Pulmonary hypertension	No	Rare	Possible	47% at diagnosis; between 50% and 90%
Desaturation on 6MWT	No	Possible	Rare	Frequent
Spontaneous improvement	Possible	Occasionally	Possible	No
Treatment	Smoking cessation	Smoking cessation and steroids	Smoking cessation and steroids?	Smoking cessation
Response to steroids	Good	Good	Fair	None
Prognosis	Good	Good	Good	Poor (5-yr survival is 55%)
Complete recovery possible	Yes	Yes	Yes	No
Correlation with lung cancer or other neoplasms	No	Rare	Frequent	Frequent (near 50%)

M: male; F: female; 6MWT: 6-min walk test; DLCO: diffusing capacity of the lung for carbon monoxide.

features overlap with other entities, such as hypersensitivity pneumonitis, the diagnosis sometimes requires lung biopsy. In the differential diagnosis between RB-ILD and hypersensitivity pneumonitis, the history (RB-ILD occurs nearly only in smokers whereas hypersensitivity pneumonitis is rare in smokers) and BAL profile (macrophagic alveolitis is observed in RB-ILD and lymphocytosis in hypersensitivity pneumonitis) are usually definitive in distinguishing between these disorders. History, HRCT and BAL findings usually allow diagnosis of RB-ILD without the need for a lung biopsy. In the appropriate clinical–radiological context, a transbronchial biopsy that shows only the characteristic aspects of RB may suggest the diagnosis of RB-ILD. By contrast, lung biopsy is generally required to diagnose DIP as the HRCT aspects of extensive ground-glass attenuation and the highly cellular BAL profile are both nonspecific [18]. It is important to remember that both DIP and RB-ILD are closely related to cigarette smoking and their histological features may be seen in association with other interstitial disease [4, 18, 41, 43]. DIP and RB-ILD should be diagnosed only in the absence of aspects suggestive of other ILDs [4, 18, 41, 43]. Patients with DIP may develop, in the long term, a HRCT pattern of fibrotic NSIP, suggesting that NSIP could be considered a new smoking-related interstitial lung disease [8]. However, the proposed relationship of DIP to fibrotic NSIP remains uncertain. The prognosis of DIP appears to be significantly better than that of fibrotic NSIP, so while there can be morphological overlap between the two, merging them into one disease may hide important prognostic information [8].

Diagnosis of PLCH

The HRCT appearance in PLCH is diagnostic in most cases. The simultaneous presence of multiple nodules, cavitated nodules and cystic spaces with an upper lung predominance and sparing of the lung bases in a young heavy smoker man is characteristic of PLCH. In end-stage disease, when only diffuse cysts with no nodules are present, the radiological diagnosis is more difficult. BAL analysis may be useful if >5% of CD1a cells are found, but this is more frequent in early stages of the disease. In the presence of a radiological cystic lung disease, macrophagic alveolitis on BAL examination may support the diagnosis of PLCH. In case of another type of alveolitis in BAL, the diagnosis should be reconsidered. In a small number of cases, the diagnosis of PLCH may be obtained on transbronchial biopsy, in the presence of the appropriate clinical and radiological setting [85, 86]. In our series of 27 patients with PLCH, transbronchial biopsy was performed in three cases and a diagnosis of PLCH was established in only one (33%) case (unpublished data). Our limited data are consistent with the literature where transbronchial biopsy is diagnostic in 10–40% of cases. Confirmation of PLCH on transbronchial biopsy requires a high index of suspicion and reliance on immunohistochemical demonstration of aggregates of LCs in the tissue [86] or the recognition of stellate scars around the bronchioles. The low diagnostic yield of transbronchial biopsy is partly due to patchy distribution of the PLCH lesions and, in advanced stages of disease, to the non-specificity of the histological features, particularly in a small biopsy sample [67, 86]. In clinical and/or radiological atypical cases, lung biopsy is necessary for a definitive diagnosis. A confounding issue in the diagnosis of PLCH by surgical lung biopsy is the exclusive presence of end-stage fibrotic changes in which LCs are scarce

or absent [87]. When this occurs, the diagnosis of PLCH may be suggested based on the histological pattern of discrete bronchiolocentric stellate scars with appropriate radiological correlation. In lung biopsies of patients with PLCH one may observe RB-/DIP-like changes as a consequence of pulmonary injury associated with cigarette smoke and occasionally these aspects may be sufficiently severe to cause ground-glass attenuation on HRCT scanning and complicate the radiological diagnosis [42].

TREATMENT AND PROGNOSIS

RB-ILD and DIP

Patients with RB-ILD usually do not need any specific treatment other than smoking cessation. Progressive evolution to fibrotic lung disease does not seem to occur and no deaths have been attributed, with certainty, to RB-ILD [5, 11]. In case of progression of disease, steroids may be useful [88]. Spontaneous improvement has been observed in some patients with DIP, possibly related to smoke cessation. There is clinical deterioration in approximately two-thirds of patients with DIP who are untreated [11, 89]. The mainstay of treatment in patients with DIP consists of corticosteroid therapy, which may cause stabilisation or improvement of the disease. Complete recovery of the disease has been described [59, 89]. In ~25% of patients, however, progression of disease may be observed despite steroid therapy [11, 59, 89] and lung transplantation may be an option. Recurrence has also been reported in patients who have received a lung transplant [90].

PLCH

Smoking cessation leads to radiological improvement and even complete recovery in early cellular and nodular cases of PLCH [89, 91, 92]. The disease may improve with smoking cessation alone; the 5- and 10-yr survival rate is 74.6% and 63.9%, respectively [93]. There have been no randomised trials comparing the efficacy of corticosteroids with that of smoking cessation alone in PLCH, and it is therefore difficult to establish the benefit of these two options. However, a subset of patients experience progressive disease; in these cases therapy still remains unsatisfactory and may include steroids and/or cytotoxic agents (methotrexate, cyclophosphamide, vinblastine, chlorambucil, etoposide and, 2-chlorodeoxyadenosine) [63, 66, 68]. Randomised trials valuating the efficacy of each of these therapies are lacking. These drugs should be reserved as salvage therapy for patients with progressive and severe disease. Recently, 2-chlorodeoxyadenosine (cladribine) was suggested as a promising treatment [94] and a randomised trial is currently ongoing in symptomatic patients with lung function impairment (www.clinicaltrials.gov NCT01473797). Patients with progressive disease associated with severe respiratory impairment and who are unresponsive to steroid therapy or chemotherapeutic agents should be considered for lung transplantation [95]. Patients should stop smoking before lung transplantation, as there is evidence of PLCH recurrence in the transplanted lung if smoking is resumed [92]. The disease may also recur in nonsmokers, especially in patients with extrapulmonary involvement [95]. The course of PLCH is variable and difficult to predict in the single patient. Prognostic factors of the disease are not well-known but obstruction, air-trapping and reduced DLCO on pulmonary function tests at diagnosis appear to be helpful in identifying patients with a poor prognosis [96, 97].

Other poor prognostic factors are older age at diagnosis and corticosteroid therapy during follow-up [96, 97]. Severe pulmonary hypertension is a frequent complication in patients with advanced PLCH. Recent observations suggest that therapy with bosentan [98] and other therapies utilised for idiopathic pulmonary hypertension may be indicated in these patients [99]. Fludeoxyglucose-positron emission tomography/computed tomography images have been proposed as a new noninvasive methodology for monitoring disease activity and response to therapy [100, 101].

STATEMENT OF INTEREST

S. Harari has relationships with drug companies including Actelion, InterMune and GSK. In addition to being an investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards.

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