Chapter 16

Smoking-related interstitial lung disease

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Summary

Cigarette smoking has a clear epidemiological association with lung diseases, characterised by chronic inflammation of both the bronchiolar and the interstitial lung compartments. There are several different smoking-related interstitial lung diseases, mainly desquamative interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease and pulmonary Langerhans' cell histiocytosis. The epidemiology of such diseases is largely unknown, although the prevalence of cigarette smoking, particularly in low-income developing countries, indicates that smoking-induced interstitial lung disorders represent a high burden of disease worldwide. The role of chest high-resolution computed tomography has become increasingly important in differential diagnosis and follow-up. A new entity, the syndrome of combined pulmonary fibrosis and emphysema, emerged as another important smoking-related lung disorder with a poor prognosis, associated with the high prevalence of pulmonary hypertension. At the moment the role of anti-inflammatory and immunosuppressive treatment remains unclear, although in clinical practice most of these patients will receive at least one course of corticosteroid therapy. It is vital to stress the importance of identifying these patients and helping them quit smoking.

Keywords: Cigarette smoke, emphysema, interstitial fibrosis, lung

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Cigarettes kill about half of all lifetime users and as such, no other consumer product is as dangerous, or kills as many people. The number of total premature deaths related to tobacco smoke worldwide exceeds 4 million each year. Tobacco kills more than AIDS, legal drugs, illegal drugs, road accidents, murder and suicide combined [1]. At the same time, cigarettes are possibly the most marketed product in the world. While there is no reliable estimate of global cigarette marketing expenditures, it is clearly tens of billions of US dollars per year [1]. Smokers have a

markedly increased risk of multiple cancers, particularly lung cancer, and are at far greater risk of heart disease, strokes, lung emphysema and many other fatal and non-fatal diseases; among these, interstitial lung disease (ILD) constitutes a clinically relevant group. The lungs and the airways are the main target of over 4,000 chemicals carried by cigarette smoke; most of these molecules have marked irritant properties and some 60 are known or suspected carcinogens. So, it is not surprising that many lung disorders have been linked to cigarette smoking for a long time. Among these, diseases affecting the pulmonary interstitium have probably been less studied than others and have only recently received the well-deserved attention due to their important clinical impact. The link between cigarette smoking and the development of ILD has been initially built around the association of tobacco smoking and the presence of these lung disorders, initially limited mainly to desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) and pulmonary Langerhans' cell histiocytosis (PLCH) [2]; another important support to the aetiological link between smoking and ILD came from the observation of clinical and radiological regression of lung involvement upon smoking cessation, in particular in RB-ILD [3]. Cigarette smoking may cause subclinical parenchymal lung disease detectable by spirometry and computed tomography (CT) imaging, even among a generally healthy cohort [4, 5]. In recent years it has become apparent that chest high-resolution CT (HRCT) scanning efficiently identifies patients affected by smoking-related ILD, being more sensitive than measurements of pulmonary function and cardiopulmonary exercise test parameters and this holds true even for subjects with asymptomatic ILD [6]. As a consequence of combined better knowledge and improved diagnostic skills, smoking-related ILD makes up a clinically relevant and challenging group of respiratory diseases worldwide. Nonetheless, knowledge in this field is constantly increasing and changing and a newly recognised causative role of smoking in several entities recently emerged. Among smoking-related diseases, physicians and radiologists will relatively often identify patients with ILD, such as PLCH, RB-ILD, DIP, acute eosinophilic pneumonia (AEP), the syndrome of combined pulmonary fibrosis and emphysema (CPFE), rheumatoid arthritis-associated interstitial lung disease (RA-ILD) or idiopathic pulmonary fibrosis (IPF). In this chapter, we will describe the main clinical and radiographic findings of these clinical entities.

Pulmonary Langerhans' cell histiocytosis

PLCH, also known as pulmonary histiocytosis X, is a disease characterised by the polyclonal accumulation of CD1a+ dendritic cells (called Langerhans' cells) in the lung [7]. This clinical entity is part of a group of systemic diseases in which involvement of other organs (such as bone, pituitary gland, thyroid, skin, lymph nodes and liver) also occurs [8]. The term PLCH identifies a disease that develops in adults, characterised by significant lung involvement with or without the involvement of other organs [9].

PLCH affects almost exclusively adult individuals in their third or fourth decades, who are either active or former smokers. Lung involvement can also be seen in Langerhans' cell histiocytosis affecting children, although this is uncommon and usually present in the context of a multisystem disease involving primarily other organs; in this case, the disease is not associated with smoking habit and its pathobiology is considered to be different from the adult smoking-related form [9].

Disease mechanisms are not fully understood. The association with smoking history in ~95% of the adults diagnosed with PLCH clearly suggests an important pathogenetic role. Cigarette smoke might activate macrophages and/or epithelial cells to produce cytokines (such as tumour necrosis factor (TNF)-α, transforming growth factor-β and granulocyte-macrophage colony-stimulating factor) that could promote either recruitment or activation of Langerhans' cells in the subepithelial regions of the airways and surrounding areas [7, 10, 11]. Specific components of cigarette smoke, such as tobacco glycoprotein, could also be involved in the direct activation of inflammatory cells in the peribronchiolar areas, thus promoting the development of the specific lesions. In addition, activated Langerhans' cells and macrophages may promote the secondary recruitment of other inflammatory cells, such as T-cells and eosinophils [7]. The disease develops

in the peribronchiolar regions and, as a result, the histological hallmark is represented by the formation of loosely formed nodules of mixed inflammatory cells surrounding the small airways, in a bronchiolocentric fashion (fig. 1a) [12]. Nodules are usually bilateral and symmetric, with predominant involvement of the upper lobes and sparing of lung bases. Initially cellular nodules evolve to fibrotic lesions with a characteristic stellate appearance and central scarring [13]. The destruction of bronchiolar walls leads to bronchiolar dilatation and cyst formation. Langerhans' cells can be identified on histology by immunohistochemical staining for CD1a (fig. 1b) and by the identification of intracellular Birbeck granules (pentalaminar rod-shaped intracellular structures) on electron microscopy. Eosinophilic infiltration is often present, particularly in the early phase of the disease [12].

While approximately 25% of patients are asymptomatic at the time of presentation, the presenting symptoms are nonspecific and include dry cough and dyspnoea [14]. Pleuritic chest pain can also be present and pneumothorax (often recurrent) is the initial manifestation in ~15% of patients. Patients with associated systemic involvement can present with additional symptoms that are related to the affected organ, particularly the skin, bone or pituitary gland.

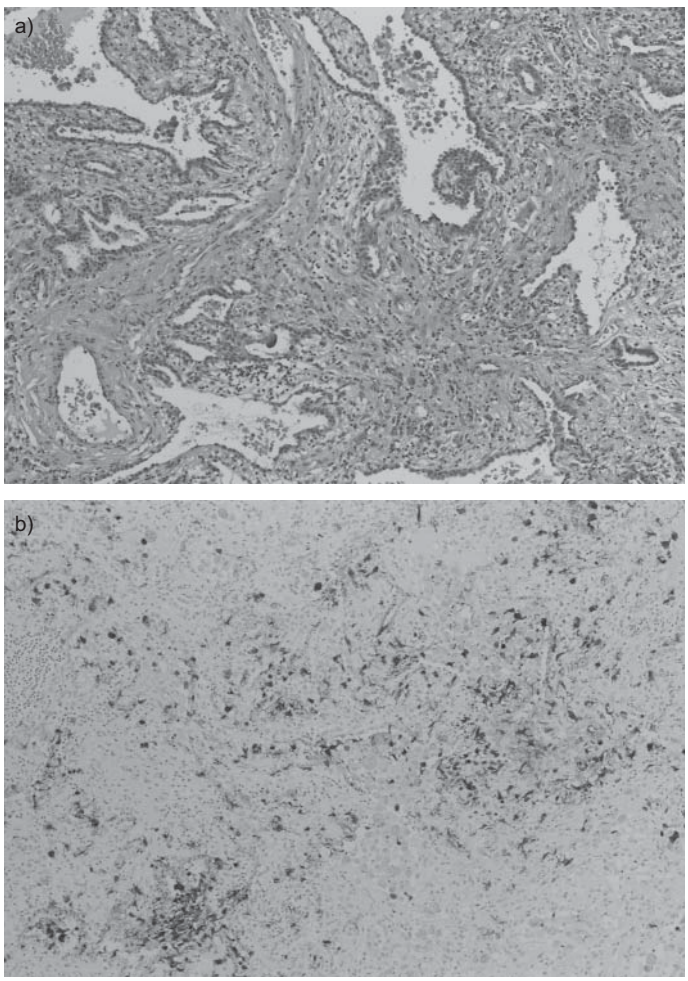

Figure 1. Pulmonary Langerhans' cell histiocytosis. a) Haematoxylin/eosin staining showing a stellariform peribronchiolar nodule with expanded interstitial spaces, type 2 pneumocytes hyperplasia and an inflammatory infiltrate comprising eosinophils and histiocytes. b) Immunohistochemistry staining showing Langerhans' cells with reniform nuclei positive for CD1a (G. Rossi, Section of Pathologic Anatomy, University Hospital Policlinic of Modena, Modena, Italy; personal communication).

Lung function tests can show either obstructive, restrictive or mixed abnormalities, even though they can be normal in the early stage. Reduced diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) is present in a large proportion of patients [14]. Limitations in the exercise capacity can occur even in the presence of mild pulmonary function abnormalities and correlate better with markers of pulmonary vascular dysfunction, as development of pulmonary hypertension (PH) may occur during the course of the disease [15].

In the presence of a proper clinical and radiological context (when the chest HRCT highlights the presence of typical features), the demonstration of an elevated percentage ($\geqslant$5%) of CD1a+ cells in the bronchoalveolar lavage fluid (BAL) is diagnostic, thus precluding the need for a lung biopsy to confirm the diagnosis [7, 16].

In the treatment of PLCH, smoking cessation is a crucial step, as it leads to stabilisation of symptoms in the majority of cases [14]. However, some patients might experience disease progression despite smoking cessation. In patients with progressive or severe diseases,

a trial with corticosteroid treatment can be considered, although data on the therapeutic benefit of corticosteroids are limited [17, 18]. Some case reports have shown a positive effect of the chemotherapeutic agent cladribine (2-chlorodeoxyadenosine, 2-CdA) in the treatment of tumour-like Langherans' cell histiocytosis with lung involvement [19, 20], as well as in patients with PLCH presenting with infiltrative disease and progressive deterioration of lung function [21]. In patients who present with pneumothorax, pleurodesis should be performed because it reduces the risk of recurrence and it is not a contra-indication for subsequent lung transplantation [22].

Prognosis is generally good with an ~13-yr median survival from time of diagnosis and 74.6% and 63.9% survival at 5 and 10 yrs, respectively [14].

Respiratory bronchiolitis-associated interstitial lung disease

Respiratory bronchiolitis is a very common finding in cigarette smokers, and was described for the first time in 1974 [23]. On histology, the typical abnormality is represented by a peribronchiolar accumulation of pigmented macrophages. Because these lesions can be observed in virtually all smokers, respiratory bronchiolitis can be considered as a histological marker of smoking. However, in 1987 [24] a new disease entity, now named RB-ILD [25], was described. The term was used to identify a disease occurring in heavy smokers, who presented with a restrictive ventilatory defect and radiological abnormalities indicative of interstitial lung disease, in which the only histological finding was represented by respiratory bronchiolitis [24].

The disease occurs in relatively young adults aged between 30 and 60 yrs, without sex predilection [26]. Virtually all patients are cigarette smokers, although a clinical syndrome indistinguishable from RB-ILD has been rarely described in subjects exposed to other sources of fumes [27, 28]. On histology, the disease is characterised by airway-centred accumulation of yellow-brown pigmented macrophages within distal bronchioles, alveolar ducts and adjacent alveolar spaces (fig. 2) [13]. Mild chronic interstitial inflammation and/or fibrosis of the peribronchiolar alveolar septa can be present, but honeycombing is uncommon [27–29]. However, there are no histological features that can distinguish RB-ILD from respiratory bronchiolitis and the definite diagnosis has to rely on a combination of clinical and radiological findings, such as symptoms, pulmonary function abnormalities and imaging (particularly HRCT). Lung biopsy can provide a definitive diagnosis, however, in the appropriate clinical and radiological context, when other causes of bronchiolar inflammation have been ruled out (including infections or exposures), there is no need for open lung biopsy [28]. In contrast, while BAL findings (increase in macrophage numbers and lower percentages of other cellular components) [30] are not diagnostic for RB-ILD, the differential cell count in BAL can be very helpful in distinguishing RB-ILD from other diseases presenting with a similar appearance on HRCT, particularly hypersensitivity pneumonitis in which BAL lymphocytosis is usually observed.

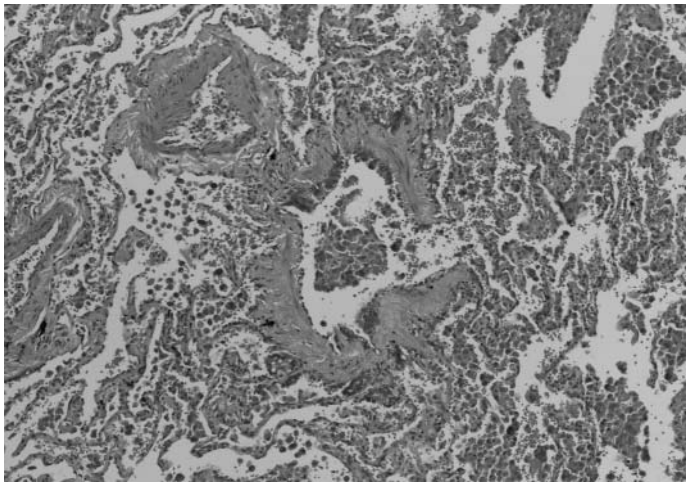

Figure 2. Respiratory bronchiolitis-associated interstitial lung disease. Haematoxylin/eosin staining showing a respiratory bronchiole with distorted architecture and accumulation of intra- and peribronchial macrophages with golden cytoplasm (G. Rossi, Section of Pathologic Anatomy, University Hospital Policlinic of Modena, Modena, Italy; personal communication).

RB-ILD prognosis is generally good and mortality is uncommon. Smoking cessation is the keystone of RB-ILD management. For

patients with mild-to-moderate disease, smoking cessation can lead to significant and consistent improvement of radiological abnormalities and lung function in a large proportion of cases [31, 32]. For patients with severe disease that does not improve following smoking cessation, a trial of corticosteroid treatment with or without associated immunosuppressive drugs is usually undertaken after a careful evaluation of risks and benefits of a prolonged treatment [24, 25, 28, 33], in fact, evidence of effectiveness for corticosteroids and/or immunosuppressive drugs is not consistent [31, 34]. Withdrawal of treatment in nonresponders is reasonable.

Desquamative interstitial pneumonia

DIP was first described by LIEBOW *et al.* [35] in 1965. In the original description, cells filling the alveolar space were thought to be desquamated alveolar epithelial cells, so the disease was termed desquamative. However, it was later recognised that cells are actually pigmented alveolar macrophages accumulating in the alveolar spaces. Macrophages accumulating in DIP appear to be identical to those seen in RB-ILD, although their distribution is different [36], in fact, RB-ILD is mainly bronchiolocentric, while DIP is characterised by diffuse involvement of pulmonary acini. Some authors would argue that RB-ILD and DIP can belong to the same clinical entity, therefore representing a continuum in the spectrum of injury associated with cigarette smoke exposure [37]. However, while RB-ILD is almost invariably associated with cigarette smoking, incidence of smoking in DIP is described in at least two-thirds of patients (60–90% in different case series), but cases of DIP associated with other causes (such as autoimmune diseases, pneumoconioses or drug reactions) have been described [38].

DIP generally presents in the fourth to sixth decade and symptoms are nonspecific, mostly characterised by insidious progressive dyspnoea and non-productive cough [31]. Pulmonary function tests show a restrictive ventilatory defect in one-third of patients and mixed defects in approximately the other two-thirds of patients, however, lung function can be normal in up to 10–20% of patients [26].

On histology, DIP is characterised by accumulation of pigmented macrophages diffusely distributed within alveolar spaces, and hyperplasia of type II pneumocytes (fig. 3) [39]. Variable degrees of diffuse alveolar wall thickening can be associated with the disease, due to fibrosis and mild infiltration of inflammatory cells. Alveolar wall architecture is preserved and honeycombing is typically absent [39]. As mentioned previously, histological findings of RB-ILD and DIP largely overlap, although a distinctive difference is in the distribution of the lesions, which are bronchiolocentric in RB-ILD and much more diffuse in DIP [40]. Also, the extent of interstitial fibrosis tends to be more prominent in DIP compared with RB-ILD [39].

A definite diagnosis of DIP can only be established on the basis of an open-lung surgical biopsy, as clinical features, HRCT and BAL findings are nonspecific [36, 40].

In the management of DIP, smoking cessation is obviously mandatory. However, unlike RB-ILD, patients with DIP can progress to respiratory failure, particularly those who continue smoking. In a series of 23 cases of DIP, three deaths from respiratory failure due to progressive diffuse lung disease have been reported [31]. Prolonged remission of DIP after smoking cessation has also been described [18]. Due to a generally more severe impairment in lung function compared to RB-ILD, early treatment with corticosteroids is usually undertaken, slowly tapered over a period of 3–6 months. However, success of corticosteroid treatment is inconsistent [31]. Immunosuppressive drugs, such as azathioprine and methotrexate, have been used in patients with DIP not responding to corticosteroids [41]. Lung transplant remains an option in patients with progressive disease and severe lung function impairment.

Acute eosinophilic pneumonia

AEP was firstly described in 1989 as an acute illness presenting with fever, hypoxaemia and possible respiratory failure, diffuse pulmonary infiltrates and increased numbers of eosinophils in

the BAL [42]. In many cases the causative agent is unknown, although a causal relationship with potential respiratory exposure has been highlighted, as patients have reported a variety of activities within days before the onset of disease, such as cave exploration, plant repotting, wood pile moving, smoke-house cleaning, motocross racing in dusty conditions, indoor renovation work and tank cleaning [43, 44]. Moreover, several cases have been reported following tobacco smoking, particularly soon after initiation of smoking or significant increase in smoking habit, with recurrence of symptoms after repeat of exposure [45–47].

AEP usually occurs in young adults (mean age of ~30 yrs), although with a wide age range [43, 44, 48]. A male predominance has been reported and the disease is not associated with prior asthma history [49].

Pathogenesis is largely unknown, existing evidence suggests that acute exposure to cigarette smoke can promote a T-helper cell type 2 inflammatory response which would promote the recruitment of eosinophils to the lung [50], which in turn can then mediate lung damage by the release of soluble factors contained in the eosinophilic granules [50].

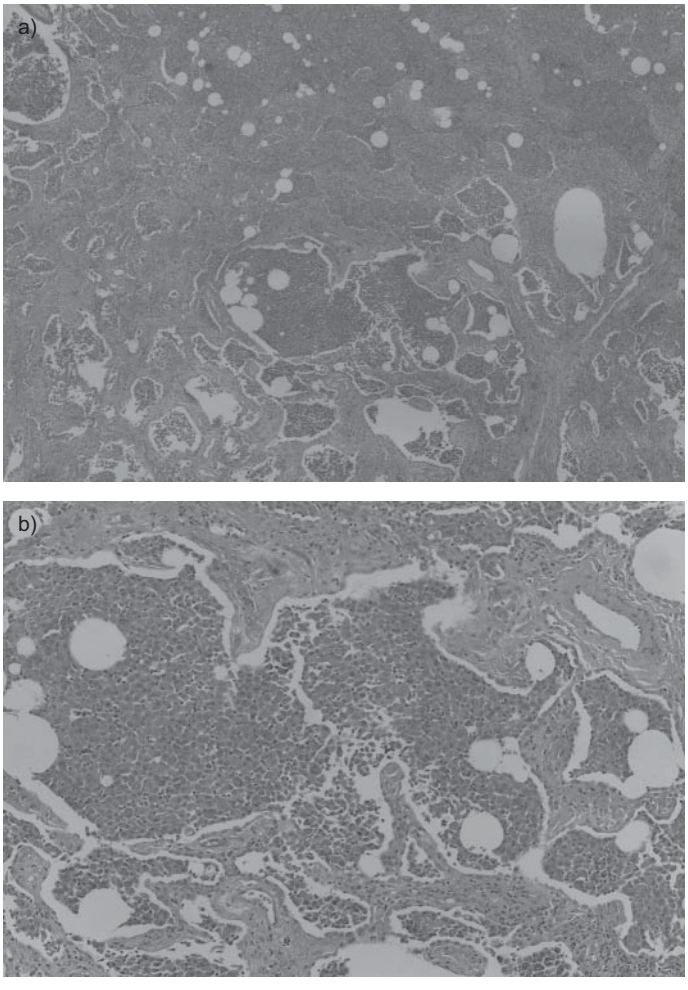

Figure 3. Desquamative interstitial pneumonia (DIP). a) Haematoxylin/eosin staining showing a fibrotic process with homogeneous involvement of the lung characterised by dense fibrosis of the interstitium and collection of macrophages into the alveoli. b) High-power view of DIP histology showing accumulation of pigmented macrophages within the alveoli (G. Rossi, Section of Pathologic Anatomy, University Hospital Policlinic of Modena, Modena, Italy; personal communication).

The disease is characterised by an acute onset, presenting symptoms are nonspecific and include cough, dyspnoea, fever and chest pain. Severe hypoxaemia can be present, with many patients fulfilling the diagnostic criteria of acute lung injury or acute respiratory distress syndrome requiring mechanical ventilation [43, 44].

In the proper clinical context, diagnosis can be made on the basis of differential cell count in BAL, with eosinophils >20% [51]. By contrast, peripheral blood eosinophil count can be normal at presentation, but generally rises to high values during the course of the disease. Transbronchial biopsy will show aspects of acute and organising diffuse alveolar damage associated with prominent interstitial and alveolar eosinophilic infiltration and interstitial oedema [52]. Although spontaneous recovery may occur, a treatment with corticosteroids is usually prescribed and leads to prompt resolution of symptoms and radiological abnormalities within weeks, without relapse [51]. The majority of patients will not have long-term sequelae, however, some patients have reported exertional dyspnoea with mild restrictive lung disease up to 1 yr later [52]. Smoking cessation should be strongly advised in patients in whom the disease was possibly associated with smoking exposure.

Combined pulmonary fibrosis and emphysema

CPFE refers to the co-existence of upper lobe centrilobular, and frequently, paraseptal emphysema (resulting from smoking) and lower lobe fibrosis (mainly of the usual interstitial pneumonia (UIP) radiologic pattern), although emphysema and fibrosis may co-occur in the same area of the lung. Physiologically, preserved lung volumes, markedly impaired diffusing capacity and hypoxaemia on exercise characterise CPFE. This syndrome is also a strong determinant of secondary PH, which, in turn, negatively affects survival [53]. The incidence of CPFE remains unknown, but it has been reported to be as high as 35% amongst patients with IPF [54, 55]. In 1990 WIGGINS *et al.* [56] described eight patients with coincidental pulmonary fibrosis and emphysema, but COTTIN *et al.* [53] were the first to report on a homogeneous group of 61 patients, all but one male and all current or ex-smokers. The median age at diagnosis, prevalence of digital clubbing (43%), presence of velcro-type bibasal end-inspiratory crackles on chest auscultation and the BAL cellular profile were similar to those observed in IPF. Spirometry and total lung capacity were normal in as many as 25% of the patients; in this regard, hyperinflation of the emphysematous areas of the lungs are likely to compensate the volume loss due to fibrosis of the lower lobes, while emphysema and fibrosis may have additive or synergistic effects on reducing the $D_{L,CO}$ and determining exercise hypoxaemia. As a consequence, CPFE may be under-recognised in patients with subnormal or normal spirometry if $D_{L,CO}$ and/or exercise blood gases are not measured. Furthermore, lung volumes, which are usually evaluated in the course of IPF, may not be relevant for the follow up of patients with CPFE. In this scenario, changes in diffusion capacity, hypoxaemia, or pulmonary artery pressure, could represent better surrogates for disease progression and mortality. The members of the French GERM"O"P (Groupe d'Etude et de Recherche sur les Maladies "Orphelines" Pulmonaires) reported the prevalence of PH to be 47% at diagnosis, although echocardiography was performed only in patients with advanced disease; thus, the study population might have been skewed towards a more severe disease phenotype, which may not represent the totality of patients with CPFE. However, NATHAN *et al.* [57] found a similar prevalence of PH (40%) amongst 118 IPF patients who underwent right heart catheterisation.

MEJIA *et al.* [55] reported that severe PH, as assessed by echocardiography (estimated systolic pulmonary artery pressure (P_{pa}) >75 mmHg) was present in 21 out of 29 patients with CPFE compared with eight out of 68 patients with IPF without emphysema ($p<0.0001$; odds ratio 19). Furthermore, 19 out of 68 "typical" IPF patients displayed normal values of estimated systolic P_{pa}, as compared with none of the IPF patients with concomitant emphysema. CPFE was also associated with shorter survival ($p=0.01$), an outcome determined by severe PH and not only by the presence of the associated emphysema [55]. Of note, in this series not only a restrictive pattern of disease was common (mean forced vital capacity (FVC) of 62% predicted) but a FVC <50% pred was also the most important variable associated with mortality, together with estimated systolic P_{pa} >75 mmHg, raising the suspicion that patients with more advanced fibrosis than emphysema may have been selected, thus hampering the generalisation of these results to the entire population of patients with CPFE. In fact, a recent report from the USA confirms that CPFE patients who are current or former cigarette smokers, have significantly larger lung volumes, have more expiratory air flow obstruction and worse gas exchange, compared with patients with isolated pulmonary fibrosis. However, in this study CPFE patients did not exhibit higher mortality [58]. COTTIN *et al.* [59] described the haemodynamic and survival characteristics of 40 patients with CPFE and PH confirmed by right heart catheterisation. Although no formal comparison could be made from this retrospective study, the authors observed that patients with PH and CPFE had a dismal prognosis, with a 60% probability of survival at 1 yr from the diagnosis of PH, which is similar to the probability of survival at 1 yr in patients with IPF and associated pulmonary hypertension at right heart catheterisation [55, 60], and worse than that of patients with chronic obstructive pulmonary disease (COPD) and associated PH [61]. Interestingly, CPFE has also been described in patients with ILD related to a concomitant connective tissue disease (CTD) [62], patients with CPFE in the context of CTD appear to be younger and more frequently female, as compared to a historical control group of patients with idiopathic CPFE.

The putative mechanisms implicated in the combination of both types of lung destruction (emphysema and fibrosis) are still largely unknown. While CPFE occurs only in smokers, many smoker patients with IPF do not develop this pathological entity. In addition, it is unclear whether emphysematous and fibrotic lesions progress independently or whether the development of one affects the progression of the other. Experimental models reveal that over-expression of TNF-α in mouse lungs provokes dramatic changes in both lung structure (airspace dilatation, consolidation and fibrosis) and function [63]. However, no differences in TNF-α expression by macrophages or bronchiolar epithelial cells have been found between IPF with and without emphysema in humans [64]. Whether the association of lung fibrosis and emphysema represents a separate clinical entity or simply a different clinical phenotype remains a matter of an intense debate. More robust evidence that the syndrome has either prognostic or management significance is now needed: specifically, it remains unclear whether the presence of emphysema has a separate effect on survival, once baseline lung function severity is taken into account [54].

Rheumatoid arthritis-associated ILD

Rheumatoid arthritis (RA) is quite a common systemic inflammatory disease that affects ~1% of the general population [65]. In RA, lung involvement is not infrequent and it can consist of various manifestations including pleuritis and pleural effusion, rheumatoid nodules, bronchiectasis and ILD [66]. ILD is certainly one of the most common manifestations of lung involvement in RA and various patterns of disease have been described [67]. In the context of CTD, terminology to describe associated ILD has been basically derived from what is used to define idiopathic interstitial pneumonias (IIPs), in fact, the same histopathological and radiological patterns that identifies IIPs, can be found in association with CTD, and a high level of suspicion is required to distinguish between idiopathic and non-idiopathic diseases. While in the majority of CTD-associated ILD the nonspecific interstitial pneumonia (NSIP) pattern is most often recognised, in RA-ILD the pattern of UIP is found to be the most common (56%), followed by NSIP (33%) and organising pneumonia (OP) (11%) [67]. Among these patterns, a diagnostic dilemma could be raised in distinguishing between UIP and NSIP patterns, particularly when a confident diagnosis of UIP pattern cannot be made on the basis of HRCT findings. However, while the importance of the distinction between UIP and NSIP is certainly well recognised in the idiopathic diseases (in which there is a prognostic correlate because survival is better in NSIP compared with UIP), whether this distinction has a clinical relevance in CTD-ILD is still an open question for the most part. In the context of RA-ILD, data available so far would suggest that patients presenting with UIP pattern have a worse prognosis (with higher risk of disease progression and acute worsening of the disease) compared with those presenting with NSIP pattern [68–70]. Moreover, patients with RA-ILD with UIP pattern seem to be less likely to respond to corticosteroid and immunosuppressive therapies [71].

In RA, articular disease generally precedes any sign of lung involvement, however, some patients may present with isolated pulmonary disease in the first place. Extra-articular disease (particular lung involvement) can be a significant cause of morbidity and mortality in RA patients [67]. The incidence of RA-ILD varies in different reports partly because of the detection methods that have been used. Also, although a fairly large proportion of patients with RA might have HRCT abnormalities consistent with ILD [72], clinically significant disease is present in a fewer number of cases, thus, according to the latest estimates, clinically significant RA-ILD occurs in nearly 10% of patients [73, 74]. A recently published paper by Olson *et al.* [74] reports the analyses of mortality data for RA and RA-ILD in a large study in the USA, which assessed all death certificates from 1998 to 2004. This study showed that, while overall mortality rates for RA declined over time (probably due to the effect of therapies), this was not the case for RA-ILD-associated mortality, particularly in the older age groups. In addition, mean age at death was significantly lower in RA-ILD patients compared with those without associated ILD and patients with RA-ILD were more likely to die of RA complications or pulmonary diseases than of other comorbidities.

Pathogenesis of RA-ILD is still not completely understood and it probably depends on both genetic and environmental factors. A higher frequency of human leukocyte antigen (HLA) B40 and lower frequency of HLA-DR4 have been reported in patients with RA and pulmonary fibrosis [75, 76]. In addition, one study showed evidence of α_1-antitrypsin deficiency in patients with RA and associated pulmonary disease [77]. Although RA is more common in females, there has been a higher frequency of RA-ILD in males with long-standing disease reported, and it has been thought that this might reflect a greater frequency of smoking in males compared with females. A relationship between smoking and RA leads to the observation that smoking is implicated in the increased risk of RA and disease severity [78, 79]. However, smoking is also the greatest environmental risk factor for lung diseases, including ILDs. Further support for the potential role of smoking in RA-ILD derives from a large study on 336 patients with RA, in which not only the severity of RA was shown to be an independent predictor of ILD, but also a significant smoking history (>25 pack-yrs) was associated with radiographic evidence and lung function abnormalities suggestive of ILD [80]. Furthermore, smoking habit seems to correlate with the type of pattern of lung involvement, as smokers tend to present with predominant UIP-like abnormalities [81, 82].

Presenting symptoms of RA-ILD are usually progressive dyspnoea and chronic dry cough and lung function generally shows a restrictive ventilatory pattern and a reduced $D_{L,CO}$. HRCT abnormalities will vary depending on the prevalent pattern of the disease, with the UIP pattern being the most common in RA-ILD, followed by the NSIP pattern [67]. There is a good correlation between the HRCT appearance and the histopathology pattern, particularly when radiologic findings are consistent with UIP; therefore, lung biopsy is not always required for the diagnosis of RA-ILD and is not routinely recommended, given the risks of a surgical lung biopsy in these patients [83].

While much progress has been made in the treatment of articular manifestations of RA, it does not seem to be the case for the management of pulmonary manifestations of the disease. At present, decisions on treatment for RA-ILD are still taken on an empiric basis [66]. Corticosteroids are often used as a first-line therapy, but results seem to be inconsistent, while histology is lacking most of the time, it appears that patients with RA associated with a NSIP pattern or OP are more likely to respond to steroids compared with those with an associated UIP pattern [71]. Experience with immunosuppressive drugs is limited: cyclophosphamide, cyclosporine, azathioprine, hydroxychloroquine and mycophenolate mofetil can be considered in the management of patients not responding to corticosteroids or as steroid-sparing agents in long-term maintenance treatment [66]. Whether TNF-α inhibitors might be useful in the treatment of RA-ILD, as they certainly have proven to be in the management of RA without lung disease, is still unclear. Some evidence seems to suggest that infliximab can lead to stabilisation of RA-ILD [84]. However, despite the introduction of these drugs, the overall mortality for RA-ILD has increased [74] and some studies have suggested that anti-TNF therapy can be associated with worsening of parenchymal lung disease [85, 86]. Lung transplantation is still an option in patients not responding to medical treatment [66].

Idiopathic pulmonary fibrosis

IPF is a chronic, progressive and lethal lung disease of unknown aetiology. The exact incidence and prevalence of this disease is unknown, but it appears to be more common than previously supposed, with prevalence ranging from 0.8 to 64.7 per 100,000 individuals and incidence ranging from 0.4 to 7.1 per 100,000 persons in the USA [87]. In the UK, the incidence of IPF has increased progressively and more than doubled between 1990 and 2003 [88]. Both the prevalence and the incidence of IPF augment markedly with age, with prevalence exceeding 175 cases per 100,000 individuals who are >75 yrs of age. Age also influences mortality and the median survival time is significantly shorter in older individuals compared with younger ones [89].

The course of the disease is variable, with many patients remaining stable or progressing slowly for long periods of time while some others exhibit an accelerated progression or experience acute exacerbations leading to respiratory failure and death [90–93]. Although there are no compelling data demonstrating that cigarette smoking is the direct cause of IPF, the majority of patients with

the disease are current or former smokers, suggesting that cigarette smoke might act together with other predisposing factors in determining the risk of disease. On surgical lung biopsy, IPF patients show a typical spatially heterogeneous pattern characterised by the presence of fibroblast foci (fig. 4). Patients with IPF are usually aged between 50 and 70 yrs, with a male predominance. The pathogenesis of IPF is largely unknown. For a long time the disease was considered the result of a chronic inflammatory reaction of the lung, followed by fibroblast proliferation/activation and finally by the exaggerated accumulation of extracellular matrix proteins. However, in 2001 a new paradigm for pathogenesis considered the epithelium as the primary site of injury and the driving force for the cascade of events that lead to lung fibrosis [94]. According to this hypothesis, alveolar epithelial cell microinjuries/apoptosis provoke the migration, proliferation and the aberrant activation of the neighbouring epithelial cells, which in turn secrete the mediators responsible for the expansion of the fibroblasts/myofibroblasts population in the IPF lungs. Source of fibroblasts/myofibroblasts in this disease might be various. Traditional thinking believed that these cells derived from proliferation of the resident pool of fibroblasts within the lung. However, two additional hypotheses have gained evidence in recent years. First of all, alveolar epithelial cells may contribute to the increase of lung fibroblasts/myofibroblasts through a phenomenon named epithelial to mesenchymal transition. Several studies have revealed the presence of lung cells showing epithelial and mesenchymal markers in IPF, transiting from alveolar epithelial cells to myofibroblasts [95, 96]. However, fibroblasts may expand through the recruitment into the lung of a particular type of circulating cells called fibrocytes. Fibrocytes are bone marrow-derived cells that share both leukocyte and mesenchymal markers (such as CD45 and collagen I, respectively) and there is growing evidence supporting their role in IPF pathogenesis and possibly as a prognostic biomarker of disease progression [97, 98]. This change of perspective in IPF pathogenesis in recent years has led to a different approach to IPF treatment from an anti-inflammatory/immunosuppressive profile to new drugs with anti-fibrotic and perhaps anti-proliferative action.

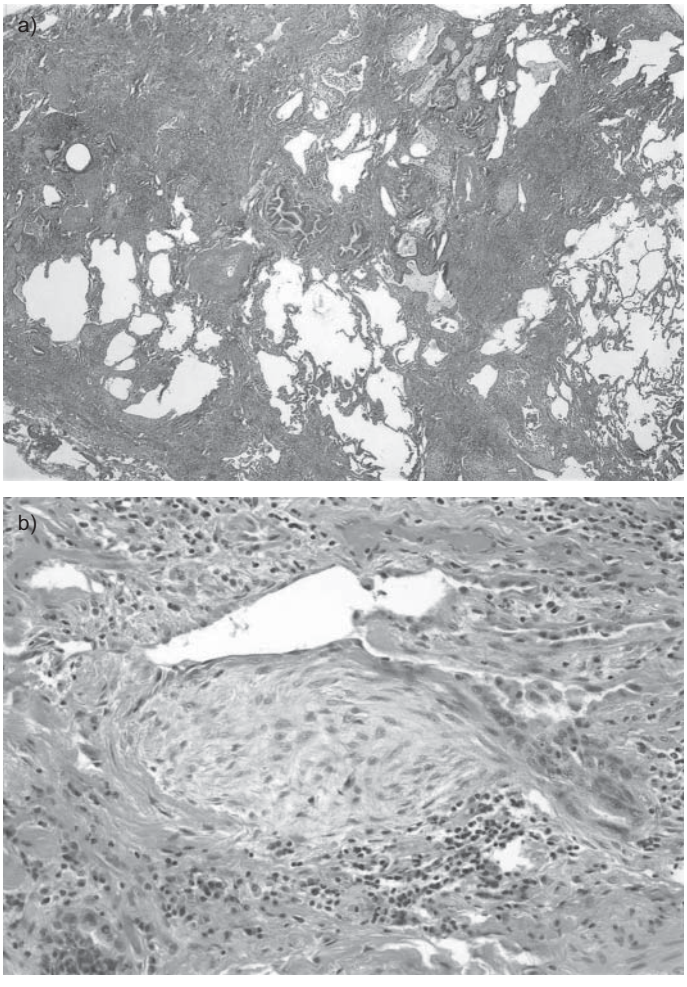

Figure 4. Idiopathic pulmonary fibrosis. a) Haematoxylin/eosin staining showing the typical chronic fibrotic process characterised by geographic/spatial and temporal heterogeneity with fibroblastic foci of active fibrosis abruptly alternating with old fibrosis and honeycombing changes. b) A fibroblastic focus at higher magnification (× 400) (G. Rossi, Section of Pathologic Anatomy, University Hospital Policlinic of Modena, Modena, Italy; personal communication).

HRCT findings in smoking-related ILDs

As with other diffuse parenchymal lung diseases, chest HRCT is more sensitive than chest radiography and, in the correct clinical setting, often suggests the diagnosis. Nevertheless, overlapping CT features

observed across the spectrum of smoking-related ILDs may confound radiologic classification into distinct entities and limit the histo-specificity of diagnoses made on HRCT.

HRCT features of RB-ILD include hazy centrilobular nodules predominating in the upper lobes and small patches of ground-glass attenuation. Centrilobular nodules and ground-glass attenuation appear to be accounted for by macrophage accumulation within respiratory bronchioles and in the alveoli and alveolar ducts, respectively [99]. In RB-ILD these abnormalities are generally widespread and often associated with a background of emphysema and bronchial wall thickening. Thickened interlobular septa due to interstitial fibrosis may be seen in RB-ILD, but they rarely represent a prominent feature. RB-ILD differs from DIP in that ground-glass attenuation of RB-ILD is usually less extensive, patchier, and more poorly defined. Conversely, peripheral subpleural and basal predominance of ground-glass opacity, reflecting either accumulation of intra-alveolar macrophages or septal thickening, is most commonly seen in DIP [37]. Small cystic spaces, which differ from those clustered of honeycombing, may develop within the areas of ground-glass opacity, and their presence increases the diagnostic confidence for DIP [100]. Honeycombing, traction bronchiectasis and architectural distortion of lung parenchyma are uncommon features of DIP. HRCT findings typical of RB-ILD effectively exclude most other diffuse lung diseases, particularly the predominantly fibrotic IIPs [36]. The combination of HRCT features of infiltrative and small airways disease is similar to that seen in subacute hypersensitivity pneumonitis and the distinction between these two conditions often rests on the smoking history because hypersensitivity pneumonitis is uncommon in smokers. However, DIP may be radiologically indistinguishable from NSIP and some cases of UIP with atypical HRCT appearance. Although HRCT may discriminate between DIP and RB-ILD the overlapping features in some cases and the occasional histological co-existence of the two entities complicates securing the correct diagnosis [37].

The HRCT features of PLCH closely mirror the macroscopic pathologic findings and depend on disease stage. The nodules, which correspond to the early small airway-centred nodular infiltrate observed histologically, are usually <5 mm in diameter, have a peribronchiolar and centrilobular distribution and may cavitate. The extent of nodular lesions correlates with the density of granulomatous lesions in the bioptic specimens [101]. In more advanced stages, the cystic-nodular pattern involving mostly the upper lobes and frequently sparing the costophrenic sulci, is virtually diagnostic of PLCH. Cysts are usually <10 mm in diameter but may coalesce becoming >20 mm and leading to bizarre-shaped spaces with a bilobed, clover-leaf, or branching appearance [102]. Nodules and cysts can occur independently of each other, but in the majority of patients they are found concomitantly. Occasionally, patchy or diffuse ground-glass opacity may be seen, probably related to areas of respiratory bronchiolitis and DIP [40]. While in typical cases HRCT appearance usually permits a confident diagnosis, end-stage PLCH may be difficult to distinguish from

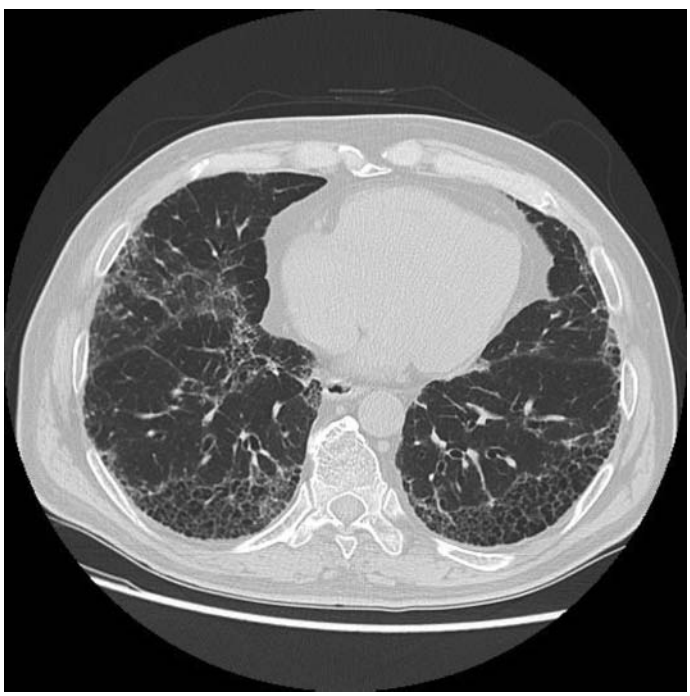

Figure 5. Idiopathic pulmonary fibrosis (IPF). Typical chest high-resolution computed tomography pattern of IPF characterised by subpleural peripheral honeycombing in the lower lobes, traction bronchiectasis and thickened interlobular septae.

other cystic lung diseases, such as lymphangioleiomyomatosis, lymphocytic interstitial pneumonia and emphysema, owing to a less obvious disease distribution [103].

The typical appearance of IPF on HRCT consists of patchy, predominantly peripheral, subpleural and bibasilar reticular opacification (fig. 5). Areas of ground-glass attenuation may also be seen but rarely represent the predominant feature. Regions of dense reticulation, which demonstrate involvement of medium-sized airways and are known as "traction bronchiectasis", are observed in more advanced disease. The presence of subpleural honeycombing, traction bronchiectasis and thickened interlobular septae constitute a highly specific radiographic pattern, termed "confident" IPF, which, in the right clinical setting, obviates the need for lung biopsy [104, 105], while less specific reticular patterns seen on HRCT and termed "possible" IPF requires surgical lung biopsy to confirm the diagnosis. However, predominant ground-glass opacities, nodular infiltrates, significant lymphadenopathy, or a predominance of upper lobe infiltrates suggest alternative diagnoses. Recently, COTTIN *et al.* [53] described a syndrome in which IPF coexists with pulmonary emphysema (CPFE). This is not surprising since both diseases are associated with a history of cigarette smoke. CPFE, the incidence of which has been suggested to be as high as 35% of IPF patients [54], is characterised by upper lobe emphysema (fig. 6a) and lower lobe fibrosis (fig. 6b).

A reticular pattern with honeycombing, and traction bronchiectasis (with architectural distortion in more severe cases) is the major abnormality in advanced disease, with ground-glass opacities being the most common findings in patients with early-onset RA [70]. TANAKA *et al.* [106] identified four predominant HRCT patterns of interstitial disease, UIP, NSIP, OP and bronchiolitis, which have proved to be excellent predictors of the underlying pathology but are indistinguishable from IIP [69, 106]. In addition, similar to idiopathic

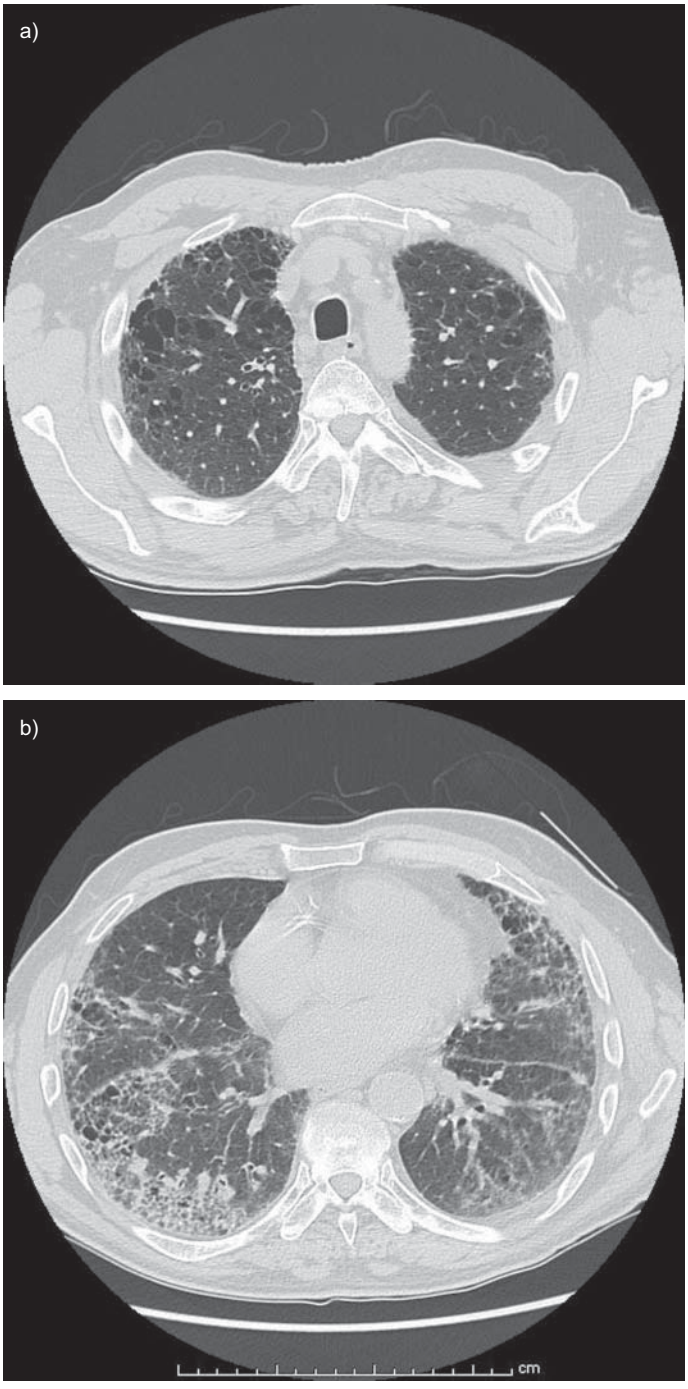

Figure 6. Combined pulmonary fibrosis and emphysema (CPFE). High-resolution computed tomography scan in a case of CPFE showing a) predominant upper lobe emphysematous changes and b) lower lobe dense fibrosis in the same patient.

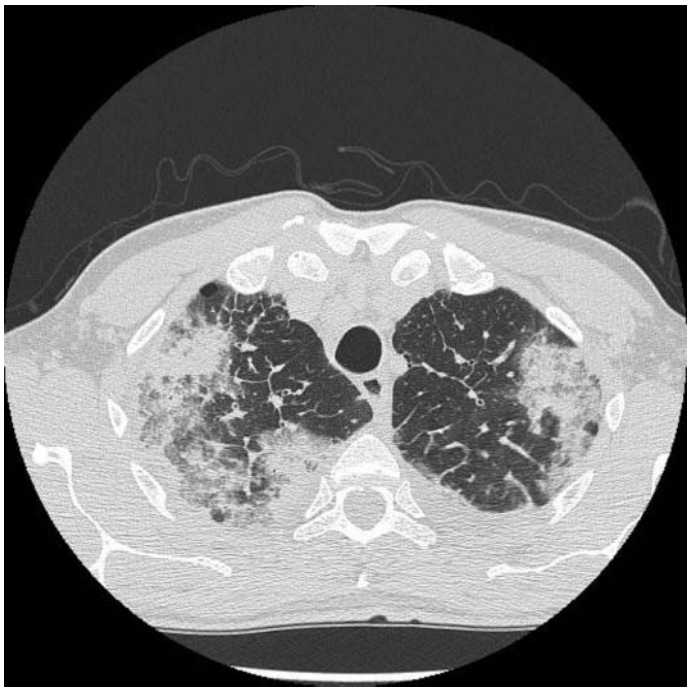

Figure 7. Acute eosinophilic pneumonia (AEP). High-resolution computed tomography scan showing bilateral ground-glass opacities and air space consolidation in a patient with AEP.

diseases, radiographic patterns appear to predict progression and outcome in RA-ILD [104]. HRCT is also important in the evaluation of airway involvement, which is common in RA. In unselected patients bronchiectasis was seen in 20–30% on HRCT [107]. The presence of centrilobular nodules, hyperinflation, and a mosaic pattern of air trapping on HRCT are highly suggestive, and their co-existence in interstitial pneumonia suggests a diagnosis of RA-ILD rather than IIP [108].

In patients with AEP, ground-glass opacities and bilateral air space consolidation are the most common patterns of parenchymal lesions on chest CT imaging (fig. 7). Poorly defined nodules and interlobular septal thickening are seen in a majority of patients, with pleural effusion, usually bilateral, being observed in at least two-thirds of patients [109, 110].

Diagnostic approach to smoking-related ILD

Clinical suspicion of a smoking-related ILD should be raised in any smoker (or ex-smoker) presenting with signs of chronic respiratory failure, *e.g.* digital clubbing and shortness of breath. Obviously, the clinical findings among the different smoking-related ILDs are nonspecific (often overlapping with the presentation of COPD) and even pulmonary function testing might be of little help in differentiating the different forms of ILD. Onset of clinical manifestations is usually insidious and gradual, with dyspnoea being the most prominent and disabling symptom. Patients commonly also complain of mild nonspecific cough, which is often attributed to smoking, thus resulting in typical delays of diagnosis. While cough is usually dry, it may also be productive of mucoid sputum, especially in advanced disease. For the majority of patients with RB-ILD, DIP, PLCH and AEP the onset of symptoms is usually in the fourth or fifth decades of life, considerably earlier than in patients with IPF. While an acute presentation is uncommon in IPF, DIP, RB-ILD and RA-ILD, AEP is a severe acute febrile illness with patients usually very dyspnoeic and hypoxaemic. Constitutional symptoms, such as weight loss, low-grade fever, fatigue, chest pain and haemoptysis may be reported in PLCH and RA-ILD, but are, otherwise, uncommon. Chest auscultation may reveal inspiratory crackles predominantly located in the lower posterior lung zones in the majority of cases. Digital clubbing is present in up to two-thirds of patients with IPF, in roughly half of those with DIP [31, 111], and only occasionally in RB-ILD [112]. In PLCH physical examination is frequently normal and auscultation of the lungs only occasionally reveals scattered crackles or wheezes, whereas in the advanced stages of the disease decreased breath sounds may be appreciated [113]. Furthermore, a minority of patients with PLCH may present with spontaneous pneumothorax, which can be bilateral or recurrent, while ~25% of patients are asymptomatic, with the disease being uncovered on a routine chest radiograph [114]. Pulmonary function test results may show a mixed obstructive-restrictive pattern with reduced diffusing capacity in RB-ILD, a marked reduction in diffusing capacity or restrictive defects in DIP, mild obstructive,

Table 1. Clinical features of smoking-related interstitial lung diseases (ILDs)

	PLCH	RB-ILD	AEP	DIP	CPFE	IPF	RA-ILD
Smoking %	>90	100		90	100	41–83	
Age	3rd and 4th decades	3rd–5th decades	2nd and 4th decades	3rd–5th decades	Middle aged and older	Middle aged and older	5th-6th decades
Male:female ratio	1:1	Slight male dominance	2:1	Nearly 2:1		1:1 to 1:2	
Occurrence in children	Rare	No	Yes	Rare	No	Rare	No
Onset	Insidious	Insidious	Acute	Insidious	Insidious	Insidious	Insidious
Presenting symptoms	Dyspnoea and cough	Dyspnoea and cough	Dyspnoea and cough	Dyspnoea and cough	Dyspnoea and cough	Dyspnoea and cough	Dyspnoea and cough
Crackles	Usually absent	50%	?	60%	Nearly all	Nearly all	Great majority
Clubbing	Rare	Rare	Rare	Nearly 50%	50–70%	50–70%	
Chest radiograph	Interstitial/cystic nodular with basilar sparing	Interstitial or normal	Patchy opacities	Interstitial, patchy ground glass	Upper lobe emphysema associated with lower lobe fibrosis	Interstitial, honeycombing with basilar predominance	Lower lobe interstitial lung disease
HRCT	Nodules and cysts; basilar sparing	Patchy ground glass	Patchy opacities /ground glass	Ground glass with lower lung predominance	Upper lobe emphysema associated with interstitial, honeycombing	Subpleural honeycombing, basilar predominance	Lower lobe interstitial infiltrates or honeycombing
Pulmonary function	Obstructive or restrictive	Mixed defect or normal	Restrictive	Restrictive	Mixed defect or normal	Restrictive	Restrictive
Treatment	Smoking cessation, steroids?	Smoking cessation, steroids	Steroids	Smoking cessation, steroids	Bronchodilators and inhaled steroids	Pirfenidone?	Steroids and immunosuppressive treatment
Response to steroids	Fair	Good	Good	Good	Poor	Poor	Variable
Prognosis	Good	Good	Variable	Good	Poor	Poor	Variable
Complete recovery possible	Yes	Yes	Yes	Yes	No	No	No

PLCH: pulmonary Langerhans' cell histiocytosis; RB: respiratory bronchiolitis; AEP: acute eosinophilic pneumonia; DIP: desquamative interstitial pneumonia; CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; RA: rheumatoid arthritis; HRCT: high-resolution computed tomography. Modified from [26].

restrictive, or mixed abnormalities with a reduction in diffusion capacity in PLCH, a restrictive defect with reduced lung volumes and diffusing capacity in IPF and relatively preserved lung volumes despite markedly impaired diffusing capacity and hypoxaemia during exercise in CPFE. Regardless of the specific entity, patients with advanced disease may have hypoxaemia at rest or with exertion. A summary of the main clinical and radiological features of smoking-related ILD is presented in table 1.

When combining all the clinical and radiological features, each of the smoking-related ILDs can be uniquely identified as the result of a combination of clinical presentations, typical HRCT abnormalities and, in some cases, characteristic laboratory findings (*e.g.* BAL differential cell count). However, in clinical practice the differential diagnosis between RB-ILD and DIP could still represent a challenge. HRCT findings typical of RB-ILD effectively exclude most of the other diffuse lung diseases, including the predominantly fibrotic idiopathic interstitial pneumonias (mainly IPF and fibrotic NSIP). There is occasional overlap in radiologic appearances between RB-ILD and DIP, although the ground-glass attenuation of DIP is usually more extensive and nodules are infrequent or absent [29, 115]. HRCT appearances of RB-ILD frequently resemble those of subacute hypersensitivity pneumonitis; in both diseases, widespread poorly formed nodular abnormalities and areas of hypoattenuation may co-exist [33, 116]. However, the combination of clinical history (RB-ILD occurs only in smokers, whereas smokers are underrepresented among patients with hypersensitivity pneumonitis) and BAL profile usually distinguishes between these two disorders [36]. In RB-ILD (and respiratory bronchiolitis alike), a characteristic brown pigmentation of alveolar macrophages has been consistently observed [36]. Moreover, BAL findings in RB-ILD differ strikingly from those of hypersensitivity pneumonitis, in which a BAL lymphocytosis is expected [117]. Therefore, BAL findings, in conjunction with clinical history and chest HRCT findings, usually allow the diagnosis of RB-ILD to be made without the need for thoracoscopic lung biopsy. By contrast, a thoracoscopic biopsy is almost invariably required to diagnose DIP, as the chest HRCT appearance of extensive ground-glass attenuation and the increased numbers of cells in BAL [30] are both nonspecific findings.

Conclusion

The fact that almost all cases of DIP, RB-ILD and PLCH occur in smokers clearly points to a direct causal role of cigarette smoking in the pathogenesis of these disorders, furthermore, a crucial role for cigarette smoking is apparent in AEP, IPF and CPFE. Currently, little is known on the pathogenic mechanisms in these disorders, although it is becoming apparent that a combination of environmental and genetic factors contributes to induction and maintenance of progressive lung damage. These non-neoplastic entities represent an important group of diseases that any chest physician will see, particularly in relatively young individuals, in the context of daily clinical practice. As such, a timely identification and an appropriate treatment, usually based on corticosteroid therapy, are of crucial relevance for these patients. Finally, an obvious consequence is the high-ranking in every physician's clinical practice of knowledge and application of state-of-the-art pharmacologic and non-pharmacologic interventions aimed at smoking cessation.

Statement of interest

None declared.

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