Interstitial lung disease related to smoking: imaging considerations

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Purpose of review
To discuss the imaging of interstitial lung disease believed to be caused by smoking.

Recent findings
It is increasingly clear that smoking is associated with a variety of patterns of interstitial lung disease. The radiologic features of interstitial lung disease caused by smoking cigarettes are variable and may be nonspecific.

Summary
It is now accepted that cigarette smoking can cause lung diseases other than lung cancer, chronic bronchitis and emphysema. Indeed, the hypothesis that tobacco smoke can cause interstitial lung disease – and, specifically, pulmonary fibrosis – dates back to the 1960s. The list of interstitial lung disease, in which smoking is believed to have an etiologic role, includes Langerhans' cell histiocytosis, respiratory bronchiolitis/respiratory bronchiolitis-interstitial lung disease and desquamative interstitial pneumonia. More recently, there is emerging evidence which suggests that smoking may be associated with other patterns of pulmonary fibrosis (e.g. nonspecific interstitial pneumonia and smoking-related interstitial fibrosis). In the present review we discuss the imaging of the interstitial lung disease known to be caused by smoking; the typical appearances and some of the diagnostic difficulties are discussed.

Keywords
diffuse parenchymal lung disease, imaging, smoking-related lung disease, tomography, X-ray computed

INTRODUCTION

The harmful effects of tobacco smoke on the lungs receive almost continuous attention in the medical literature and the nonmedical press. This is with good reason because lung cancer and chronic obstructive pulmonary disease (COPD) are the two most serious sequelae. At a global level, lung cancer accounts for around 1 million deaths annually [1] and World Health Organization estimates suggest that the prevalence of COPD exceeds 60 million [2]. The imaging of lung cancer and COPD has been extensively covered in the literature and is not in the scope of the present review.

Over the past two decades – driven in no small part by increasing insights from radiologic studies – interest has focussed on the relationships between cigarette smoke and interstitial lung diseases. The extant literature provides evidence of the links between smoking and the entities of respiratory bronchiolitis/respiratory bronchiolitis-interstitial lung disease, desquamative interstitial pneumonia (DIP) and pulmonary Langerhans' cell histiocytosis (LCH). In addition to the well-known entities, there is ongoing debate about the aetiological role of tobacco smoke in the pathogenesis of lung fibrosis. In the present review we will consider the imaging of the recognized smoking-related interstitial lung diseases. In addition, we will discuss some of the thinking behind other lung disorders now thought to be causally associated with smoking.

SMOKING-RELATED INTERSTITIAL LUNG DISEASES: DISCRETE OR OVERLAPPING ENTITIES?

When classifying diseases, one approach is to 'lump' entities together based on their shared

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KEY POINTS

- There is a recognized association between smoking cigarettes and the development of interstitial lung disease.
- Imaging tests (and particularly, CT) have a role in diagnosis of smoking-related interstitial lung disease.
- The radiologic findings in smokers with interstitial lung may be nonspecific and mixed patterns are not infrequently encountered.

characteristics. The other would be to 'split' individual disorders into more discrete groupings. However, rigid classification systems can prove frustrating, particularly when attempting to define patterns of disease that naturally overlap. From what follows in this review, it could be argued that smoking-related lung damage represents a continuum of pathologic processes. Indeed, pathologists often find a mixture of histopathological patterns in biopsy samples and find it difficult to make a single pathologic diagnosis. In LCH, elements of emphysema and other smoking-induced pathologies are not uncommon both in biopsy specimens [3,4] and on imaging studies (Fig. 1). In other patients with LCH, there is florid macrophage infiltration which makes the distinction from DIP impossible [5]. The task of a making a pathological diagnosis of emphysema might, on first thought, be assumed to be easy; the pathologist must confirm that there is air space dilatation with destruction of the walls while excluding obvious fibrosis [6]. However, the requirement to exclude obvious fibrosis can be problematic, particularly when one considers that there may be evidence of fibrosis on biochemical [7,8] and radiologic [9] grounds in some patients.

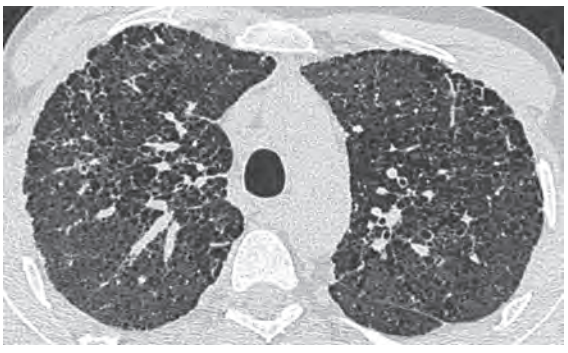

FIGURE 1. Mixed CT patterns caused by smoking. Image at the level of the aortic arch demonstrates multiple thin-walled cysts, widespread ground-glass opacification and centrilobular emphysema. A diagnosis of Langerhans' cell histiocytosis with coexistent desquamative interstitial pneumonia was made at biopsy.

The waters are further muddied because it has long been postulated that cigarette smoke can cause both emphysema and lung fibrosis [10–12]. Indeed, the relationship between smoking and lung fibrosis is the subject of renewed speculation; even a cursory glance at the literature reveals a multitude of terms – probably describing overlapping/interlinked pathologies – now used to describe patterns of lung fibrosis in smokers [13,14,15▪▪,16]. One such entity is 'combined pulmonary fibrosis and emphysema' [17–19]. However, the question about whether combined pulmonary fibrosis and emphysema represents a separate clinico-pathological-radiologic entity (with an unusually high incidence of pulmonary hypertension) or simply the coexistence of emphysema and lung fibrosis in smokers [20] still provokes debate.

SMOKING-RELATED INTERSTITIAL LUNG DISEASES

The following sections describe the smoking-related interstitial diseases. The characteristic imaging features of LCH, respiratory bronchiolitis and respiratory bronchiolitis-interstitial lung disease (RB/RBILD), and DIP will be reviewed. Areas of difficulty in establishing a radiologic diagnosis of these disorders will be also highlighted.

PULMONARY LANGERHANS' CELL HISTIOCYTOSIS

Classification issues and histopathologic considerations

LCH is just one of a group of dendritic disorders in which there is infiltration of organs by Langerhans' cells [21–23]. The expansion in the Langerhans' cell population is clonal and it has been suggested that LCH may represent a neoplastic proliferation [21,24]. The reported associations between LCH and some cancers (typically lung and haematological [25–28]), and the more recent discovery of oncogenic mutations in BRAF and MAP2K1 [29▪,30,31] in LCH, lend support to the hypothesis.

The historical classification of LCH was not satisfactory: localized disease of a single organ or structure was called eosinophilic granuloma, whereas multisystem forms were given eponymous labels including Hand–Schüller–Christian disease, Hashimoto–Pritzker syndrome and Letterer–Siwe disease [22]. More recently, the terminology has been simplified [21,32] and the only important

division is between single organ and multisystem disease [21,22]. Moreover, irrespective of the primary target, the diagnosis is simply that of 'LCH', appended with the name of the involved organ(s). Pulmonary LCH occurs either in isolation (the more common scenario) or as part of multisystem disease [28,32].

The unifying feature in all forms of LCH is the Langerhans' cell, so named because of the similarity to cells in the skin that contain Birkbeck granules. Langerhans' cells are distinct from other cells of dendritic lineage by virtue of CD1a antigen expression and a novel transmembrane glycoprotein called langerin [33]. It is now widely accepted that cigarette smoke has an etio-pathogenic role in pulmonary (but, importantly, not other forms of) LCH: well over 90% of patients with pulmonary LCH are smokers [4,28,34]. Experimental data have also linked components of cigarette smoke to the development of pulmonary LCH [35–37].

On histopathologic examination, the earliest finding in the lungs is bronchiolocentric interstitial infiltration [3,5,38]. In time there is progression and the infiltrate becomes more nodular and individual nodules contain Langerhans' cells, eosinophils, lymphocytes and fibroblasts. There may be marked DIP-like macrophage infiltration in the surrounding air spaces. Cavitation of nodules is typical and, in some cases, the cavity is connected to the lumen of a dilated airway [38,39]. The defining histopathological lesion of LCH is a nodule with a star-like or stellate border and central scarring [3]. Another characteristic finding in pulmonary LCH is the temporal heterogeneity so that cellular lesions often coexist with focal scarred nodules. End-stage pulmonary LCH is typified by confluent scarring associated with widespread emphysema, the latter simulating honeycombing.

Imaging of Langerhans' cell histiocytosis

Chest radiography

In established disease, there is usually a diffuse abnormality on chest radiographs: a reticular pattern with micronodules (measuring up to 2 mm in diameter) are the main findings [40,41]. Although they are an important feature on computed tomography (CT), the confident identification of cysts is difficult on plain radiography because of anatomical superimposition. Disease is usually most marked in the mid and upper zones and there may be relative sparing of the lung bases. A useful radiographic sign is that apparently extensive disease on chest radiography may still be associated with preserved – or sometimes even increased – lung volumes (Fig. 2). Pleural effusions, lymph node enlargement, endoluminal masses and a solitary pulmonary nodule are all reported but less common manifestation of pulmonary LCH [40,42–44].

On serial radiographs, nodules can regress (sometimes spontaneously) and this may be in response to smoking cessation [45,46]. In some patients there is relapse after a period of apparent stability, [47] whereas in others there is slow but unabated progression, occasionally complicated by airflow obstruction and pulmonary hypertension [48].

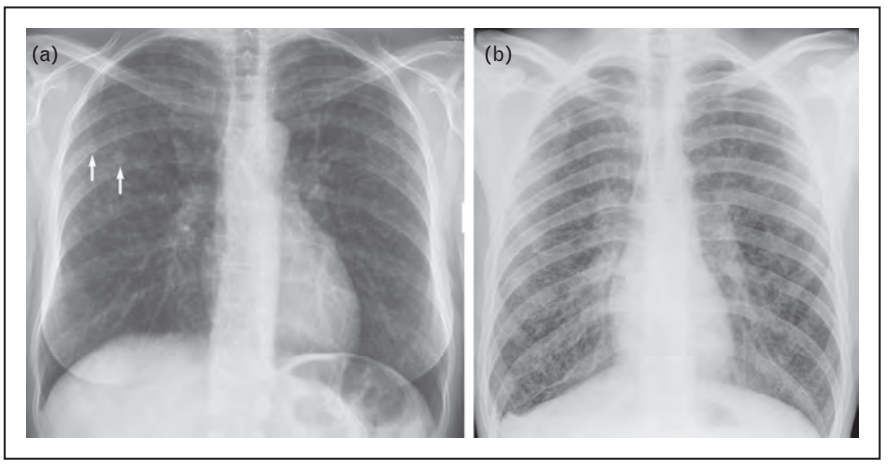

FIGURE 2. Chest radiographs in two patients with Langerhans' cell histiocytosis. (a) There is symmetrical abnormality with multiple nodules in the mid/upper zones and relative sparing of the lower zones; two nodules in the right lung are cavitating (arrows). (b) A diffuse reticular pattern in both lungs – there is no apparent sparing of the lung bases but note that despite extensive reticulation, the lung volumes are increased.

Computed tomography

LCH is more easily characterized on CT than plain chest radiographs. However, it is salutary that, in a few patients, CT may be entirely normal despite histologically proven disease [49], possibly representing rare 'occult' cases of pulmonary LCH [50]. In the classical case, there are nodules and thin-walled cysts [49,51]. Nodules and cysts tend to be seen together and the occurrence of cysts or nodules in isolation is relatively uncommon [51]. The CT appearance, at any time-point, will reflect the phase of the disease: nodules tend to be more prevalent in the early stages of the LCH but, over time, the profusion of cysts increases [52]. Nodules in LCH can be very small (measuring up to 5 mm in diameter; Fig. 3), have irregular margins and correspond to the inflammatory granulomatous lesions seen by pathologists [49,52,53]. Some nodules appear to be centred on pulmonary lobules although, in reality, this relationship to the lobular core structures is not always apparent on CT [51]. At some point, nodules inevitably cavitate and, on serial CT examinations, the typical sequence of nodules cavitating and eventually forming thin-walled cysts becomes clear [52] (Fig. 4). Cysts may be small to begin with (typically less than 1 cm in diameter) with a wall which varies in thickness from barely perceptible to several millimetres.

In contrast with other disorders characterized by cysts, a useful CT sign (presumably caused by the coalescence of adjacent lesions) is that cysts in LCH can have unusual (i.e., not rounded) outlines (Fig. 5). Another important clue is the relatively sparing of the lung bases and the tips of the middle lobe and the lingula [49]. The bizarre outline of some cysts when combined with nodules and the characteristic distribution should help the radiologist to differentiate LCH from lymphangioleiomyomatosis [54–56]. In the latter, cysts tend to have a more conventional rounded shape and a relatively uniform distribution with no zonal predilection. In some patients, the distinction between emphysema and LCH can be surprisingly difficult, a problem compounded by the coexistence of emphysema in smoking patients with LCH [49,52]. In general, the low attenuation foci of emphysema usually lack a definable wall [57]. However, when the lesions of centrilobular emphysema extend to the periphery of the pulmonary lobule, it is easy to see how the differentiation may not be straightforward.

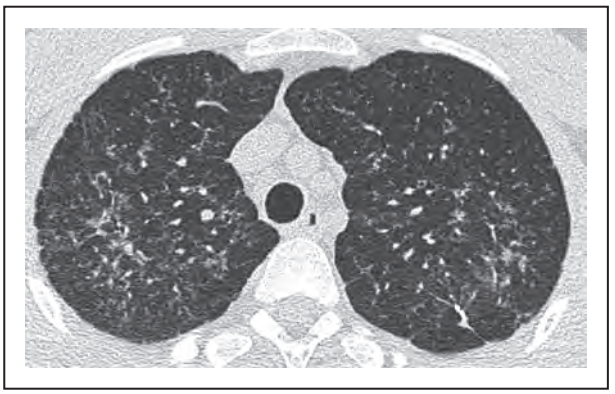

FIGURE 3. CT image through the upper lobes showing a micronodular pattern in pulmonary Langerhans' cell histiocytosis.

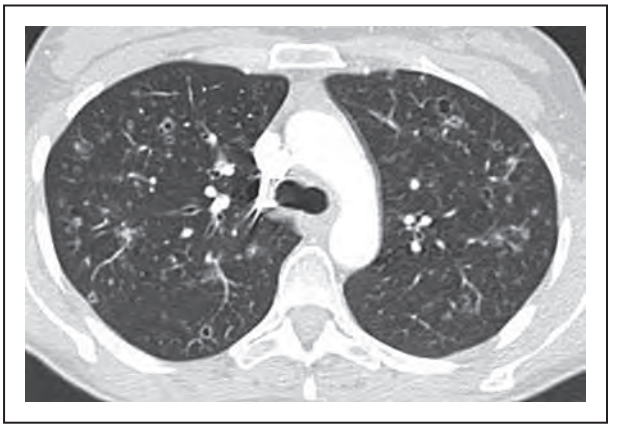

FIGURE 4. CT at the level of the aortic arch in a young female smoker. There are multiple nodules a few of which are clearly cavitating; the walls of cavities vary in thickness. Note that there is centrilobular emphysema of limited extent in both upper lobes.

DESQUAMATIVE INTERSTITIAL PNEUMONIA, RESPIRATORY BRONCHIOLITIS AND RESPIRATORY BRONCHIOLITIS-INTERSTITIAL LUNG DISEASE

Historical and pathological perspectives

DIP was first recognized by Liebow almost 50 years ago [58]. The key finding was that of uniform air space filling by 'large cells' which, at that time, were presumed to have been shed or 'desquamated' from alveoli. However, this view has long been discarded and it is clear that the cellular infiltrate of DIP – similar to that in RB/RBILD – comprises macrophages with characteristic 'glassy' cytoplasmic pigmentation [59,60]. It is also perhaps worth reiterating that DIP is no longer believed to be an early (cellular) phase of idiopathic pulmonary fibrosis [61–64]. The relationship between cigarette smoke and DIP is reasonably strong [62,65] but, unlike RB/RBILD (in which a smoking history is

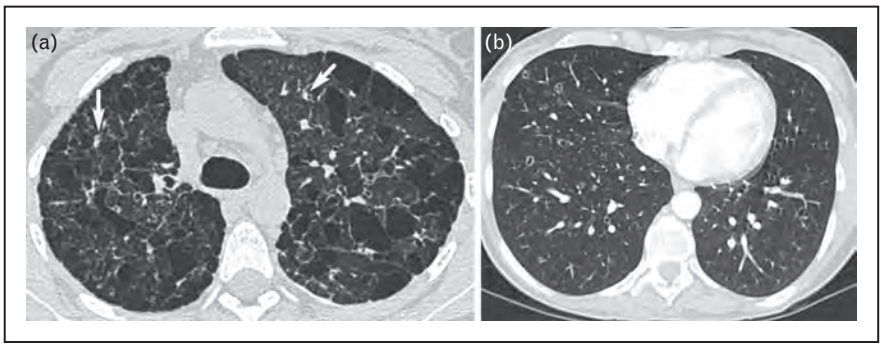

FIGURE 5. Two patients with Langerhans' cell histiocytosis showing characteristics CT features. (a) Image section through the upper lobes shows multiple thin-walled cysts, many with curious shapes; note that even with this apparent 'end-stage' appearance, scattered small irregular nodules (arrows) are still visible. (b) CT through the mid-zone (in the same patient as in Fig. 4) showing sparing of the tips of the middle lobe and lingula. There is minimal disease in the lower lobes.

almost inevitably present [66]), there are reports of DIP occurring in nonsmokers [67–70].

The histopathologic lesion of respiratory bronchiolitis was first reported by Niewoehner *et al.* [71] as an incidental postmortem observation. In the original paper, the authors described the characteristic finding in 19 of 39 individuals, all of whom were smokers. It seems likely that respiratory bronchiolitis of variable extent is present in the lungs of all smokers and that it may persist (sometimes for decades) after smoking cessation [66]. It is also worth stressing that the overwhelming majority of patients with respiratory bronchiolitis are asymptomatic, albeit with mild (but subclinical) physiologic impairment [71,72]. A small minority of patients with pathologic respiratory bronchiolitis present with the clinico-radiologic and physiologic picture of an interstitial lung disease and it is for these patients that the diagnostic label of RBILD is used [65,73].

As suggested above, there are both similarities and differences in the microscopic appearances of DIP and RB/RBILD [60,65,70,74▪]. The unifying feature is the presence of typical pigmented (smokers) macrophages. In DIP, the infiltration is diffuse and the alveolar septa are thickened by inflammatory cells, which include eosinophils, plasma cells and lymphoid follicles [60,70]. Interstitial fibrosis in DIP is usually mild but generally more severe than in respiratory bronchiolitis [70]. A more important distinguishing feature between DIP and respiratory bronchiolitis is that, in the latter, the infiltrate and accumulation of intraluminal/alveolar macrophages is strikingly bronchiolocentric. In summary, the two key differences between RB/RBILD and DIP, are first, the extent of involvement and second, its distribution. However, despite this apparently simple distinction, it is clear that there are overlapping appearances which makes the histopathologic separation of these entities difficult [5,65,75].

IMAGING OF DIP AND RESPIRATORY BRONCHIOLITIS AND RESPIRATORY BRONCHIOLITIS-INTERSTITIAL LUNG DISEASE

Plain chest radiography

The historical term 'dirty lung' was loosely applied to describe the appearance of a coarse basal reticular pattern on chest radiographs in some smokers. However, the relationship, if any, between this somewhat enigmatic descriptor and the now recognized smoking-related lung diseases is unclear [76–78]. In the original report by Liebow, ground-glass opacification in the lower zones was the dominant radiographic abnormality in the majority of patients with DIP [58]. In two later series, a reticulo-nodular pattern was the most common abnormality with ground-glass opacification being less frequent [61,62]. Not surprisingly, in some patients, the chest radiograph is entirely normal [58,62,65].

The chest radiograph may be also normal in just under one-third of patients with RB/RBILD [65,73] or, at most, show subtle changes. In an earlier study of radiographic appearances in smokers and nonsmokers, a reticulo-nodular pattern (possibly representing RB/RBILD) was the dominant abnormality in smokers [76]. A diffuse but fine reticulo-nodular pattern was present in four of six patients in Myers' original series [73], and this is largely corroborated by subsequent reports [65,75,79] (Fig. 6). Ground-glass opacification is uncommon in RB-ILD. There was no evidence of ground-glass opacities in any of the 18 patients in one study [65] and was a dominant feature in only three of 10 patients in another study [75].

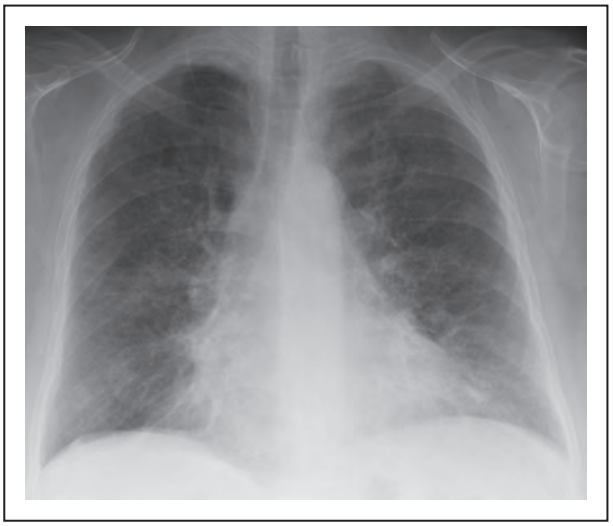

FIGURE 6. Chest radiograph in a patient presenting with breathlessness and an abnormal gas transfer. There is a diffuse bilateral reticulo-nodular pattern consistent with a diagnosis of respiratory bronchiolitis-interstitial lung disease.

Computed tomography

DIP is exceedingly rare and an indicator of this is that one of the largest historical studies of DIP comprised only 22 patients culled from the medical records at five centres over 8 years [80]. The predominant abnormality on CT is diffuse ground-glass opacification resulting from the accumulation of macrophages in the alveoli [79–81] (Fig. 7). Mid and lower zone involvement is typical and there is a predilection for the subpleural lung (although the distribution of ground-glass opacification can be entirely random) [79]. Other findings include irregular lines together traction bronchiectasis, parenchymal distortion, cysts, emphysema and parenchymal nodules [80]. Honeycombing is an uncommon finding [82].

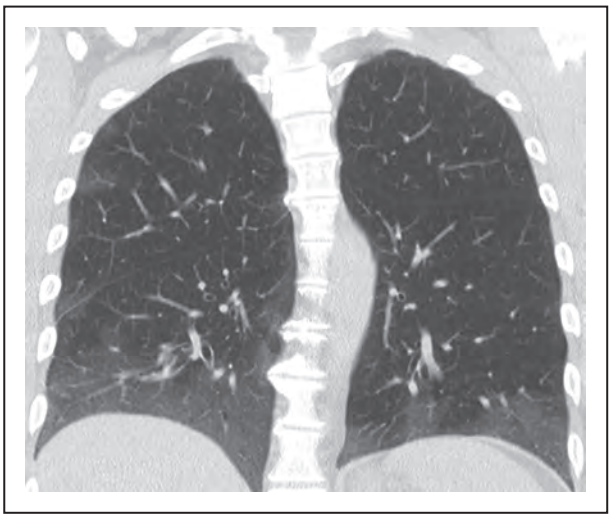

FIGURE 7. Desquamative interstitial pneumonia on CT. Coronal reconstruction showing relatively 'bland', nonspecific ground-glass opacification in both lower lobes. There were no convincing CT features of established fibrosis in this patient.

From the above description, the reader will no doubt gather that the CT appearances of DIP are nonspecific and a confident diagnosis of DIP may not be forthcoming, even from experienced thoracic radiologists [83]. In most cases, DIP has a favourable outcome [62] and, on serial CT examinations, ground-glass opacities tend to regress with corticosteroid therapy [63,81,84].

The CT findings in patients with RB/RBILD vary in terms of the frequency of specific patterns and also in the zonal distribution [75,79,85]. The common findings are ill-defined centrilobular nodules with central and peripheral bronchial wall thickening [86] (Fig. 8). Ground-glass opacification of variable intensity is also often present. Patchy foci of lobular decreased attenuation (reflecting the bronchiolitic component) is a less common but tell-tale sign in RB/RBILD. Emphysema (which is rarely extensive) may also be present in the upper zones. Thickening of interlobular septa is a feature in some patients [75,79,85].

On the basis of the discussion above, it will be clear that CT appearance of RB/RBILD and DIP overlap [79]. Poorly defined nodules and regions of ground-glass attenuation are common findings RB/RBILD [79,87]. Furthermore, diffuse ground-glass opacification (a relatively consistent finding at CT in patients with DIP and RBILD) is a wholly nonspecific sign on CT, caused by diseases in the airspaces and/or the interstitium [88,89]. Accordingly, the distinction between RB/RBILD and DIP is ideally based on multidisciplinary evaluation after considering the available clinical/physiologic, radiologic and histopathologic data.

One area of diagnostic difficulty is in distinguishing RB/RBILD from subacute hypersensitivity pneumonitis. Common features in both are ill-defined centrilobular nodules, ground-glass opacification and lobular regions of low attenuation [90–92]. In this setting, the smoking history may tip the balance because of the supposed 'protective' effect of tobacco smoke against hypersensitivity pneumonitis [93]. In reality, multidisciplinary evaluation often needs to consider other factors including the possible role of inciting antigens, gas transfer indices and, where available, the cellular profile of bronchoalveolar lavage fluid.

CIGARETTE SMOKING AND PULMONARY FIBROSIS

The hypotheses linking cigarette smoke to pulmonary fibrosis date back to the 1960s [10,94]. In 1963,

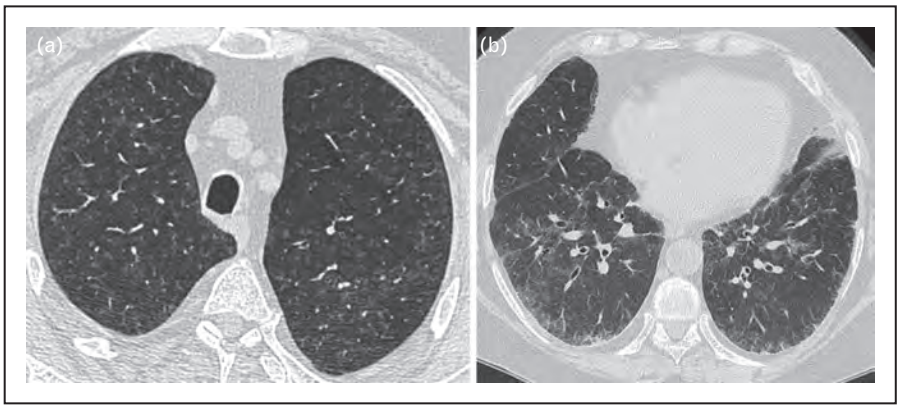

FIGURE 8. Typical CT appearances in RB/RBILD. (a) CT through the upper lobes demonstrates multiple 'soft' centrilobular nodules and patchy ground-glass infiltration. (b) Image through the lower zones in another patient showing, in addition to ground-glass opacities, thickened interlobular septa, lobular regions of decreased attenuation and some thick-walled subsegmental airways.

Auerbach *et al.* [94] reported fibrosis in the alveolar septa of smoker's lungs. It could have been argued that such changes were related to age except for the fact that all histopathological abnormalities were more common in smokers. Since this early observation, there has been considerable debate about the associations between smoking and different patterns of fibrotic lung disease [10,12,13,15▪▪,16,62,95–101]. In two of the earliest publications, the majority of patients with idiopathic pulmonary fibrosis [IPF; then still called cryptogenic fibrosing alveolitis (CFA) outside of North America] gave a smoking history [62,102]. However, it is stressed that these studies were published well before the American Thoracic Society/European Respiratory Society consensus classification of idiopathic interstitial pneumonias [60] and, it seems inconceivable that the cohorts studied in the late 1970s and 1980s were a 'pure' group of patients with IPF. That said, it has long been known that CT in many patients with IPF/CFA will show concomitant emphysema [20,103], a combination which, incidentally, can lead to interpretative difficulties (especially when emphysema merges with fibrotic honeycombing in the mid and lower zones) [104].

The pathogenetic link between smoking and lung fibrosis is unlikely to be confined to IPF. There are some grounds for believing that a pattern of nonspecific interstitial pneumonia (NSIP) might be caused by smoking in some patients [70,105] (Fig. 9). In a retrospective review by Craig *et al.* [70], initial and follow-up HRCT in a small number of patients with DIP, showed appearances more akin to NSIP. In another study looking for indirect links between smoking and NSIP, the investigators found a higher than anticipated prevalence of emphysema in current/ex-smokers with NSIP as compared to a cohort of 'healthy' smokers with normal physiology [105]. Interestingly, there seemed to be a difference (albeit in small numbers) in the morphological patterns of NSIP between nonsmokers and those with a smoking history: a crazy paving pattern of NSIP was seen in seven of 10 nonsmokers but in only two of 19 current/ex-smokers [105].

Other patterns of lung fibrosis, hitherto unclassified, have also been reported in smoker's lungs. For instance, Katzenstein [15▪▪] have shown that clinically silent (but pathologically significant) fibrosis is present in the lungs of smokers. In their histopathologic study of lobes resected for cancer, there was 'significant' fibrosis in 18 of 20 patients with a smoking history and, strikingly, in none of the lifelong nonsmokers. The patterns of fibrosis varied but the most common finding (seen in nine cases) was alveolar septal thickening caused by relatively thick bundles of acellular of hyalinized collagen and relatively minimal inflammation. There was evidence of emphysema and features of respiratory bronchiolitis (occasionally severe) in all cases. The histopathologic findings of this lung fibrosis could not be classified as one of recognized patterns and the authors have coined the name smoking-related interstitial fibrosis [15▪▪,16]. Whether this pattern of fibrosis will, in time, become recognized as a distinct form of smoking-related lung injury is not clear.

CONCLUSION

Tobacco smoke is known to be harmful to the lungs. Interest in the aetiological role of cigarette smoke and a variety interstitial lung diseases continues. Indeed, many disorders known to be linked to smoking have been well characterized and radiology has contributed to this. However, challenges remain not least because of the known propensity for overlap and the coexistence of different smoking-related pathologies. Indeed, for some patients, the generic

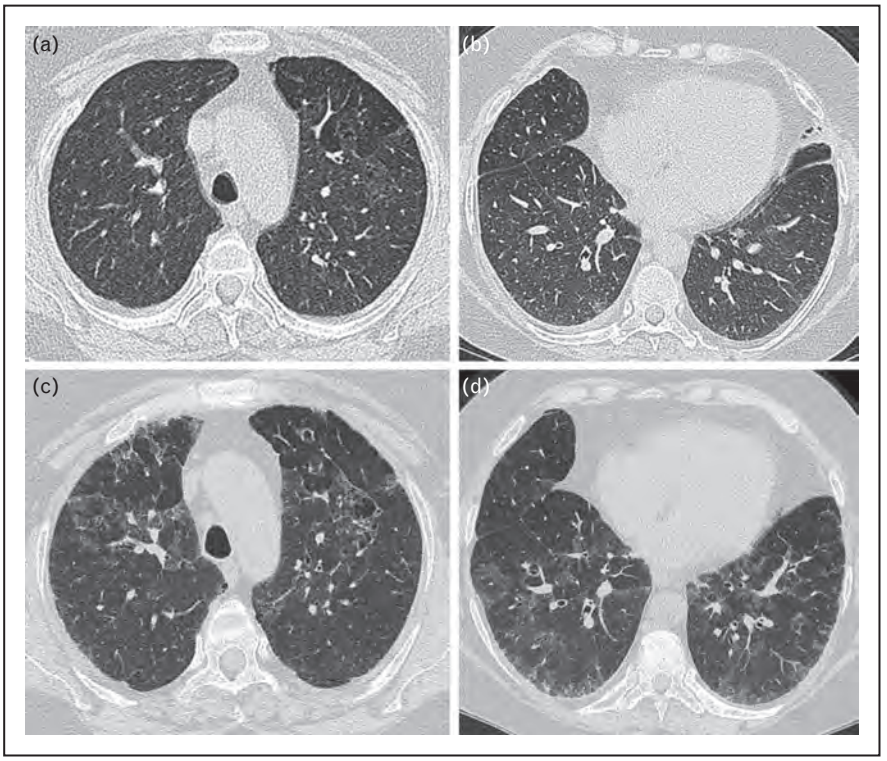

FIGURE 9. Progressive smoking-related interstitial lung disease: (a,b) Images through the upper and lower lobes respectively in 2005 compared with (c,d) images of comparable anatomic sections from 2012. There has been a progressive increase in the extent of ground-glass opacification (particularly in the lower lobes), fine reticulation, lobular decreased attenuation and limited emphysema. Subtle traction bronchiectasis is seen in the right lower lobe in 2012. A clinico-radiologic multidisciplinary diagnosis of suspected smoking-related interstitial lung disease was made.

label 'smoking-related interstitial lung disease' may be the most appropriate. More recently, attention has shifted to the possible linkages between cigarette smoking and pulmonary fibrosis. Imaging tests continue to have an important role not only in clinical evaluation but also in unravelling the possible pathogenetic mechanisms underlying the smoking-related interstitial lung diseases.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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