

## Respiratory bronchiolitis associated with interstitial lung disease and desquamative interstitial pneumonia

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This article explores issues of the diagnosis and management of respiratory bronchiolitis (RB), respiratory bronchiolitis-associated interstitial lung disease (RBILD), and desquamative interstitial pneumonia (DIP). These three diseases have common and overlapping features (Table 1) and sometimes are viewed as a continuum of smoking-induced disease, rather than as distinct and separate entities [1]. The constellation of overlapping features makes definitive statements difficult but we conclude with some guidelines about how these disorders might be considered.

### Disease definitions

#### *Respiratory bronchiolitis*

RB is a common incidental finding on histopathologic examination of lung samples that are obtained from heavy smokers. Pigmented macrophages accumulate within respiratory bronchioles and adjacent alveoli [2], with a characteristic histopathologic picture of peribronchiolar inflammation and fibrosis that was first described in 1974 [3]. These features, usually found in asymptomatic individuals, often are incidental findings on lung biopsy or at postmortem. Whether this entity should be viewed as a disease or

as a normal response to smoking remains unclear despite much debate. Even more contentious is the question of when RB crosses the boundary to become RBILD, in which the mixture of histopathologic features is identical to those in respiratory bronchiolitis. It has been argued that when the problem becomes clinically evident through symptoms (often difficult to dissect out from other manifestations of smoking, such as bronchitis or emphysema) or abnormal imaging or pulmonary function tests, the term “RBILD” should be used; however, this implies that interstitial lung disease is always present in the context of these clinical features.

#### *Respiratory bronchiolitis-associated interstitial lung disease*

In 1987, Myers et al [4] described the features of six heavy smokers who had lung crackles on auscultation, a restrictive ventilatory defect, and chest radiographic abnormalities that were compatible with interstitial lung disease. At open lung biopsy, clusters of macrophages were evident in and around terminal bronchioles; the surrounding alveolar septa were thickened with a mild chronic inflammatory cell infiltrate. These abnormalities also were reported in subsequent series [5,6]; the clinical distinctions between RB and smoking-related interstitial lung diseases can now be refined. RBILD is a clinically overt smoking-related interstitial lung disease in which the essential histopathologic features are indistinguishable from smoking-related RB where the patient largely is symptom-free.

When does respiratory bronchiolitis become respiratory bronchiolitis-associated interstitial lung

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Table 1  
Summary of key features

Features	RB	RBILD	DIP
Lung function	–	+	++
Macrophages within airspaces	+	+	++
Granular pigmentation within macrophages	+	+	+
Histologic bronchocentricity	++	++	–
Ground-glass on HRCT	+/–	+	++
Alveolar septal thickening on HRCT	+/–	peribronchial	diffuse
Honeycombing and fibroblastic foci on HRCT	–	–	–
Micronodular abnormalities	+	++	–
BAL	Pigmented macrophages	Pigmented macrophages	Pigmented macrophages, Variable neutrophils or Variable eosinophils

—, not present/no change; +, increase/present; ++, large increase/significant feature.

disease? We suggest that the diagnosis of RBILD requires a combination of significant pulmonary function abnormalities and compatible findings on high-resolution CT (HRCT) that are more than limited in extent. The same HRCT and histopathologic abnormalities have been classified as RB or RBILD in different series, which creates confusion. The diagnosis of RBILD should not be made using pulmonary function abnormalities or HRCT in isolation. The same individual HRCT features are reported in studies of healthy smokers and in RBILD; the only difference is the extent of abnormality. Diagnostic differentiation is difficult to standardize based solely on the extent of HRCT abnormalities. Similarly, the pattern of impairment of pulmonary function differs from the changes that are seen with other smoking-induced pathologic disorders. The combination of definite (rather than trivial) disease on HRCT and lung function abnormalities that are not attributable to any other clearly identifiable lung disease (especially smoking-induced lung disease), taken together with the pathologic lesion of RB, define RBILD. This can be contrasted with smokers who have RB and identical histopathologic features to those of RBILD and (usually limited) abnormalities, such as centrilobular nodules, on HRCT despite normal lung function tests.

#### *Desquamative interstitial pneumonia*

DIP also has been linked to RBILD; any discussion of DIP must include RB and RBILD. DIP and RBILD are considered by some investigators to represent a continuum of smoking-related inflammatory disease, in view of their similar pathology and almost invariable association with cigarette smoking

[1]. There are sufficient differences between RBILD and DIP to defer final judgment, however [7].

#### **Histopathology**

The histopathology of RBILD and RB are identical. The main feature is the accumulation of alveolar macrophages within respiratory bronchioles, with the infiltrate extending into neighboring alveoli. Macrophages are characterized by glassy eosinophilic cytoplasm with light brown and finely granular pigmentation that often is superimposed and is believed to represent constituents of cigarette smoke. Foamy macrophages are not a feature of these disorders.

Generally, a chronic inflammatory cell infiltrate in bronchiolar and surrounding alveolar walls occurs. More variably, thickening of the peribronchial alveolar septal by fibroblasts and collagen deposition is present which typically radiates from the involved bronchiole [8]. This feature often is absent in asymptomatic RB and even in symptomatic RB it is much less severe than in RBILD.

Because of a perception that fibrotic damage and inflammatory infiltration that extend from the peribronchiolar regions into the surrounding alveolar septa are more prominent in RBILD, the diagnosis primarily was histopathologic in several series [1,6,9]. With the advent of HRCT, however, it is clear that RBILD varies considerably in severity throughout the lung; sampling error (ie, variation in morphologic severity depending on the site of the biopsy) is a major confounder. Therefore, the distinction between RB and RBILD should not be based upon histopathologic evaluation alone, but on global

severity, as judged by HRCT and pulmonary function tests.

Fibroblastic foci and honeycomb change are not features and, when present, a coexistent disease process is likely. Pulmonary parenchyma, distant from involved airways, often shows hyperinflation or overt emphysematous change, but may be normal [10].

The histopathologic severity of RB differs surprisingly little between current and ex-smokers [11,12], although nonsignificant trends have been observed in which smokers have more extensive disease and ex-smokers have less macrophage pigmentation [11]. One explanation for the apparently paradoxical similarity between ex-smokers and current smokers is selection bias; histopathologic evaluation may be more likely to occur in ex-smokers who have prominent smoking-related symptoms. Thus, a dichotomy in disease behavior following cessation of smoking may exist; a large subgroup may have rapid regression of RB but another subgroup may have persistent disease [11].

DIP is characterized histopathologically by diffuse alveolar septal thickening, hyperplasia of type II pneumocytes, and intense accumulation of intra-alveolar macrophages [13]. Unlike RBILD, macrophage distribution in DIP is diffuse and not bronchiolocentric; however, macrophages do contain pigment which is identical to that seen in RBILD and RB [14]. Areas of DIP-like reaction that are histologically indistinguishable from DIP were observed in association with more widespread RB or RBILD [11]. This observation highlights the concept that smoking-related disease processes often coexist.

Future studies need to focus on the interrelationships between these disorders, particularly on the assessment of longitudinal behavior that might determine whether RB/RBILD evolves to emphysema, as was observed recently in an HRCT study [15]. Another key question is whether RB evolves to RBILD and then to DIP, and if so, how frequently. Current data suggest that this is not the case.

### Smoking relationship

RB has been associated almost invariably with smoking. The largest histopathologic study reported the clinical and pathologic features of 109 cases of RB that were identified from review of 156 consecutive surgical lung biopsy specimens [11]. Of the lung biopsy specimens, 107 had RB, including all 83 current smokers and 24 of 49 ex-smokers (49%). RB persisted for many years after stopping smoking; it

occurred 5 years after quitting in one third of patients and 32 years later in one patient. There was a correlation between pack-year smoking history and the level of cytoplasmic pigmentation of macrophages; the presence of peribronchial fibrosis was associated with a higher pack-year smoking history. Five cases of variant RB were identified (these resembled RB in that accumulation of macrophages in small bronchioles and surrounding airspaces occurred, but differed from classical RB lesions in that no cytoplasmic pigment could be identified). All five cases occurred in patients who had never smoked and the significance of this observation is unknown. The conclusion from these investigators and from other studies that were reported subsequently, is that RB is a highly sensitive and specific morphologic marker of cigarette smoking. No independent association with gender or age has been found.

It is widely accepted that RB is confined to smokers, despite the fact that in the landmark autopsy series of Niewoehner et al [3], 20% of patients who had RB were nonsmokers. In this series, the smoking histories for the patients were necessarily taken from relatives; it is not clear that smoking was excluded rigorously. Peribronchial pigmented macrophages also may accumulate in dust-related environmental lung diseases, but generally are associated with dust macules/nodules or other features that are indicative of an exposure other than cigarette smoking. The lower prevalence of RB in smokers in earlier histopathologic series [16,17] compared with the series of Fraig et al [11] is likely to reflect differences in histopathologic diagnostic criteria and the grouping together of current and former smokers in analysis. Overall, RB is seen in less than half of former smokers who have stopped smoking for more than 6 months [11]. The more recent consensus—that RB is present to some degree in all current smokers—is likely to be based soundly because the large series of Fraig et al [11] can be viewed as definitive.

The speed with which RB clears after the cessation of smoking seems to be variable. Serial bronchoalveolar lavage (BAL) studies [18,19] showed that, in some cases, 3 years is required to return pigmented macrophages to nonsmoker levels. In these reports, it is likely that unusually prolonged involvement was studied selectively. Fraig et al [11] observed that a significant proportion of ex-smokers had no RB less than 1 year after stopping smoking and, in contrast, there was persistence of RB decades after stopping smoking in other instances. The extent to which this surprising variation represents differences in macrophage (host) responsiveness is uncertain.

There seems to be an equally striking causative link between smoking and RBILD. In the three largest clinical series [4,6,9], almost all patients were current cigarette smokers, although a single non-smoking patient who had a heavy exposure to solder fumes in the workplace was reported [9]. There is a wide reported age range with no gender predilection.

In DIP, most patients are smokers, including 36 of 40 patients (90%) in the largest series [20]. DIP is seen more frequently in nonsmokers than RBILD, however, and has been observed in pneumoconiosis, rheumatologic disease, and drug reactions [8,21–24].

## Investigations

### *Pulmonary function testing*

The functional impairment in RBILD varies between clinical series [4,6,9]. The common picture is a mixed, predominately restrictive pattern with a moderate reduction in DLCO, despite the bronchiolecentric nature of disease.

Although the level of functional impairment is a defining diagnostic feature that distinguishes RBILD from RB, it remains unclear why some patients who have moderately extensive fibrotic change that radiates from bronchioles have little or no abnormality of their pulmonary function parameters [11]. Possible explanations include sampling error and the normal variation in baseline functional measures; in patients who had presmoking functional indices of 110% to 120% of predicted, substantial loss in pulmonary function may occur without levels decreasing to less than the “normal range”.

By contrast, in some patients who have RB or RBILD, functional impairment may be unexpectedly severe. The frequent existence of concurrent emphysema is a major confounder in the interpretation of pulmonary function tests. Emphysema may result in an obstructive picture and, as seen in other fibrotic conditions [25], may combine to give near normal lung volumes. The combination of emphysema and RBILD can lead to a disproportionate reduction in DLCO [4,9], sometimes less than 60% of predicted. Thus, although pulmonary function test abnormalities are a key part of the distinction between RB and RBILD, the pattern and level of functional impairment should not be used in isolation to make this judgement. In DIP, the pattern of abnormality is restrictive with reduced DLCO; often, patients present late with striking hypoxia.

## Radiology

In RB, the chest radiograph usually is normal or of limited diagnostic value. Even in RBILD, where bronchial wall thickening and areas of ground-glass attenuation are frequent on chest radiography [26], HRCT is clearly the defining radiologic modality (Fig. 1).

HRCT has been used to investigate the lung parenchyma of smokers for the last 10 to 15 years. In current smokers, parenchymal micronodules and areas of ground-glass attenuation were significantly more prevalent than in nonsmokers [27]. Parenchymal micronodules were ill-defined and tended to be more profuse in the upper zones. Limited HRCT abnormalities, which should be regarded as signs of RB and not RBILD, are not associated with functional impairment, except when emphysema also is present. Large series in current smokers underline the difficulty in distinguishing RB from RBILD based on the nature of HRCT abnormalities. It is clear that HRCT findings in RBILD occupy the same spectrum as those in RB, although they generally are more prominent.

Early descriptions of HRCT findings in RBILD were influenced heavily by the belief that the diagnosis should be based on histopathologic appearances. It seems to be inevitable that misclassification occurs between RB and RBILD, especially when regional variation in disease severity results in sampling error. This problem is likely to explain highly variable HRCT reports, with the range of appearances in RBILD encompassing centrilobular micronodules, ground-glass attenuation, atelectasis, linear reticular abnormalities, emphysema, and a normal pattern [1,28–30]. Even until 1997, it was

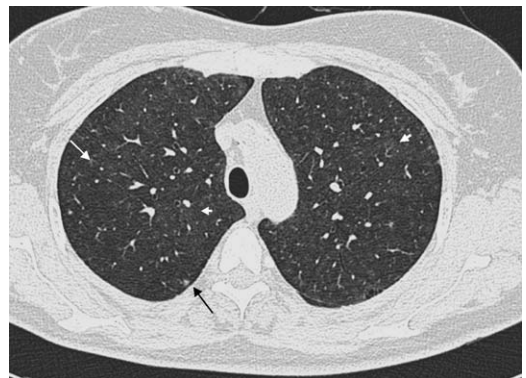


Fig. 1. CT showing numerous poorly-defined centrilobular nodules (arrows) and patchy ground-glass attenuation in a bronchovascular distribution (arrow heads).

believed widely that most patients who had RBILD had normal HRCT appearances [31], with the paradoxical observation in one series that the HRCT features were less striking in RBILD than in RB [1]. This view is now difficult to sustain and is not compatible with the suggestion that the severity of disease on HRCT should be a pivotal diagnostic determinant in RBILD. In a more recent report of a large number of patients who had RBILD, overt HRCT abnormalities were the rule, including thickening of airways proximal to segmental bronchi, peripheral bronchial wall thickening distal to segmental bronchi, centrilobular nodules, and areas of ground-glass attenuation [26]. Centrilobular nodules (degree of macrophage accumulation within respiratory bronchioles and the severity of chronic inflammation within the respiratory bronchiolar walls) and ground-glass attenuation (amount of macrophage accumulation in the alveoli and alveolar ducts) was diffuse with no zonal predominance, as compared with RB and DIP. The range and severity of abnormalities did not differ greatly between current and ex-smokers.

Areas of hypoattenuation (mosaic attenuation) occur in RB and RBILD, but seem to be less prevalent in the former, in keeping with less severe HRCT changes generally. Mosaic attenuation on HRCT is a cardinal feature of small airways disease, as reported in constrictive bronchiolitis [32], hypersensitivity pneumonitis [33], bronchiectasis [34], and sarcoidosis [35]. In a large study of 250 volunteers (191 current or ex-smokers), mosaic attenuation was detected rarely on inspiratory HRCT but was disclosed on expiratory HRCT in 62% of subjects [36]. Limited lobular air trapping on expiratory HRCT was present in 47% of subjects, did not vary with smoking status, and probably can be viewed as a normal finding [37]. Segmental and lobar air trapping were significantly more prevalent in current smokers (26%) and ex-smokers (27%) than in nonsmokers (8%). Areas of ground-glass attenuation, overt emphysema, and ill-defined micronodules were frequent findings in smokers; the last characteristic often was associated with air trapping which established that mosaic attenuation is part of the characteristic HRCT profile of RB.

In early series, HRCT distinctions between RBILD and RB must be interpreted with caution, with the additional caveat that the significance of mosaic attenuation (which is often subtle) might not have been appreciated. Furthermore, the identification of mosaic attenuation, as a marker of small airways disease, is problematic in the setting of patchy ground-glass attenuation; expiratory HRCT,

which seldom is performed routinely, often is required to identify gas trapping. Thus, the apparent absence of mosaic attenuation in most studies [1,27,38] is not altogether surprising; however, in the most recent series which may be the only definitive HRCT description of RBILD, mosaic attenuation was obvious on inspiratory HRCT in more than 35% of cases and had a lower lung predominance [26].

A recent study of serial HRCT findings showed that significant changes on serial HRCT were evident only in persistent smokers [15]. The prevalence of emphysema increased (26% to 40%), with a similar increase in the frequency of ground-glass attenuation (28% to 42%), over a mean period of 5.5 years. Micronodular abnormalities, which were present in 19 persistent smokers at initial scanning, increased or were unchanged in 14 cases. In 5 cases, profuse micronodules were replaced by emphysema. The first report of apparent evolution from RB to emphysema may have major pathogenetic implications for chronic obstructive pulmonary disease. The fact that this was observed in only 5 patients should be emphasized; the observation needs to be reproduced in larger patient cohorts.

The HRCT features of DIP were reported in only one sizeable series, which required participation by several centers (reflecting the rarity of the disease). Ground-glass attenuation was present invariably and was bilateral, symmetric, and predominately basal and peripheral in half of cases [39], unlike the nonzonal nature of abnormalities that were observed in RBILD (Fig. 2) [1,26]. In many other cases,

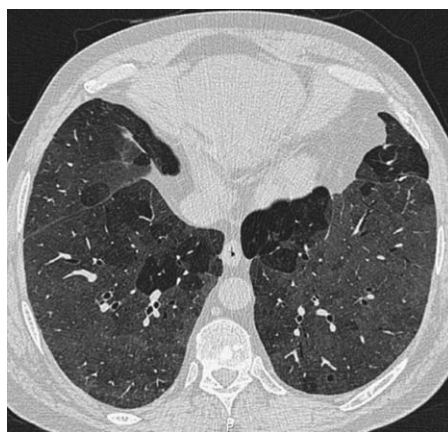


Fig. 2. CT showing widespread ground-glass attenuation, predominantly at the bases and classic for DIP. Note little evidence of architectural distortion or traction bronchiectasis.

however, no predominant zonal distribution was apparent. This underscores the important caveat that DIP never should be excluded based upon HRCT distribution of disease. Irregular linear opacities were seen in more than 50% of cases. These were predominantly basal and associated with anatomic distortion, traction bronchiectasis, and small peripheral cystic spaces, which are believed to represent dilated bronchioles and alveolar ducts. These features, which are considered to indicate pulmonary fibrosis, usually are limited in extent. Honeycomb changes that are typical of usual interstitial pneumonia (UIP), are not an HRCT feature either at presentation or at follow-up. In a recent series that included long-term follow-up in a small subgroup, HRCT characteristics that resembled fibrotic nonspecific interstitial pneumonia was present; fixed ground-glass attenuation was admixed with fine reticular abnormalities and contained traction bronchiectasis [24]. The importance of this finding relates to the contention by some investigators that RBILD and DIP are an HRCT continuum and that the two diseases should be unified as a single disorder [1]. The recent observation that RBILD and DIP might evolve in different ways, to emphysema and interstitial fibrosis, respectively, is a powerful argument that terminologic unification of these disorders is premature. It should be stressed, however, that a great deal more work is required on the longer-term findings in both diseases.

#### *Bronchoalveolar lavage*

BAL plays an important part in the diagnostic process. The characteristic increase in brown-pigmented macrophages, a consistent finding in RBILD, does not distinguish between RBILD and RB but it does help to exclude other forms of interstitial pneumonias (eg, DIP, UIP, and fibrotic nonspecific interstitial pneumonia [NSIP]) [40]. In RBILD, a mild neutrophilia may be present, but eosinophilia or lymphocytosis do not occur. This aids differentiation from other lung diseases, such as hypersensitivity pneumonitis or lymphocytic interstitial pneumonia with coexistent follicular bronchiolitis that have similarities in HRCT appearance but in which a high lymphocytosis is found at BAL [41]. The integration of HRCT, clinical, and functional findings helps to distinguish RBILD from other lung diseases, and ultimately, with increasing experience, should reduce the need for thoracoscopic lung biopsy to make the diagnosis.

Furthermore, BAL in DIP has a completely different pattern from RBILD; this provides addi-

tional support that they are distinct diseases. Generally, increased lymphocytes or neutrophils, with or without increased eosinophils, are found in DIP.

#### *Thoracoscopic lung biopsy*

The combination of HRCT, pulmonary function testing, and BAL is allowing some diagnoses to be ascertained without the need for thoracoscopic lung biopsy. The major indications for a thoracoscopic lung biopsy are:

- Doubt about the diagnosis, especially in ex-smokers
- HRCT evidence of concurrent pulmonary disease, including fibrosis
- To exclude more progressive forms of idiopathic interstitial pneumonia
- To rule out more extensive fibrotic change than is evident on HRCT

#### **Clinical features at presentation, prognosis, and treated course**

In RBILD and DIP, the most frequent presenting features are the insidious onset of exertional breathlessness and a persistent cough that is not always productive of sputum [6,9,10,14]. Chest pain and systemic symptoms, including weight loss and fatigue, also can be present. Bibasilar end-inspiratory crackles are present frequently but clubbing is rare. The diagnoses of RBILD and DIP are made on the basis of the pattern of disease and demonstration of imaging and functional abnormality; therefore, the presence of symptoms has no impact on the diagnostic process.

Although RBILD and DIP are regarded as benign disorders, both may be associated with extensive fine fibrosis; severe hypoxemia during single-lung ventilation was described in a patient who had RBILD [42]. Despite this and the paucity of definitive longitudinal pulmonary function data, it is clear that DIP and RBILD have a better outcome than other forms of idiopathic interstitial pneumonia [20,43], especially idiopathic pulmonary fibrosis and fibrotic NSIP [44]. Regression of RB occurred in most patients in one study [11], but other studies showed variable lung function trends [9] and an inconsistent response to steroid and immunosuppressant treatment and smoking cessation [9,45]. Although the inflammatory component of RBILD may abate with time, associated fibrotic change, which may be more

extensive in RBILD than in RB, may be a major determinant of enduring functional impairment. In DIP, therapeutic outcomes generally are good although there are instances of longer-term fibrosis.

The therapeutic approach tends to be governed largely by the level of pulmonary function impairment in RBILD and DIP. As spontaneous regression of disease may occur, it is generally accepted that a period of observation following smoking cessation is warranted, except in functionally severe disease. An empiric trial of therapy, however, has been the norm in most series when abnormalities are severe or do not regress following smoking cessation. A further important contributor to lack of therapeutic response in some cases is the presence of coexistent emphysema. A fatal outcome of RBILD has not been reported [43].

Therapeutic experience has been confined to agents that are used in other forms of idiopathic interstitial pneumonia, notably corticosteroids, with or without immunosuppressive agents [4,6,9,10,26,45]. A response to therapy should not be expected in RBILD (unlike DIP) and the benefits of prolonged treatment with attendant side effects have yet to be established. Response to treatment is believed to be restricted to a small minority; therefore, early cessation of treatment in nonresponders often is appropriate, unless functional impairment is severe. It is hoped that longitudinal studies with larger cohorts of patients who have RBILD will emerge in the next few years. In DIP, it generally is possible to taper the dosage of corticosteroids from the starting level of 40 mg to 60 mg (given for 4–6 weeks) to cessation over a 6- to 9-month period, depending on response. Occasional patients who have DIP without major associated fibrotic disease do not respond to corticosteroids or immunosuppressive agents.

### Difficult clinical issues

We are left with some uncertainties. HRCT will allow DIP (ground-glass attenuation being more intense and regional) [8,46] and more progressive forms of idiopathic interstitial pneumonia (UIP, fibrotic NSIP) to be distinguished from RBILD. There may, however, be difficulties in separating RBILD from subacute hypersensitivity pneumonitis; widespread poorly formed micronodular abnormalities and regional hypoattenuation can occur in both diseases [26,33]. In such a case, the smoking history is vital because subacute hypersensitivity pneumonitis is uncommon in current smokers. BAL is

particularly helpful; a lymphocytosis favors hypersensitivity pneumonitis and a marked increase in macrophage numbers is a hallmark of RBILD. It is unusual to need to perform a surgical biopsy to make this distinction.

Another major confounder is the common coexistence of several different disease processes that can be found in cigarette smokers. It is important to tease out the coexistence of processes and evolution from one to another; to establish the dominant process, if possible; and to recognize the importance of cessation of cigarette smoking in patients who have a full constellation of features. Our hypothesis is that smoking-related inflammation precedes and leads to irreversible damage.

### Are desquamative interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung disease the same disease?

The overlap in histopathologic and HRCT features in some patients led to the postulate that a morphologic continuum exists from asymptomatic RB, through RBILD, to DIP [7,8]. Despite the attraction of a simplification of terminology, however, recent consensus statements tended to classify RBILD and DIP as separate entities, although they have many common features, including smoking, HRCT, and histopathology [47,48]. Reasons for continued separate classification include:

- Exact severity criteria for a diagnosis of RBILD have not been formulated. The diagnosis of RBILD, by contrast with RB, has varied from study to study. Merging RBILD with a third disorder, DIP, in which the disease generally is severe, has the potential to add to the current diagnostic confusion;
- No current evidence that progression occurs from RBILD to DIP [49].
- The possibility that these disorders may evolve into different smoking-related lung disorders (eg, RB/RBILD to emphysema) [15].
- Overt pulmonary fibrosis is evident on HRCT in DIP in more than 50% of cases [1,39], but was reported in only a few patients who had RBILD [6,28].
- Therapeutic strategy in RBILD, in which the value of treatment may be marginal in many cases, contrasts with the more vigorous approach that usually is appropriate in DIP.
- Different BAL profiles of the two diseases.

Until the pathogenetic significance of these differences has been clarified, DIP and RBILD can be regarded as useful, separate entities.

### A suggested schema

RB should be considered as a normal consequence of cigarette smoking that is present to some degree in all smokers and often is associated with cough. If present, HRCT and pulmonary function abnormalities are necessarily mild (more severe abnormalities equate to RBILD).

RB-interstitial lung disease can be viewed as unusually severe RB and requires for diagnosis:

Moderately extensive typical HRCT abnormalities AND

Reduced lung volumes and gas transfer, in the absence of, or out of keeping with HRCT features of coexisting smoking-induced disease (NSIP, Langerhans' cell histiocytosis, or emphysema), although occasionally, elements of all three of these smoking-induced diseases may coexist.

Generally, DIP is extensive with a widespread (and often predominately basal) increase in attenuation on HRCT that is not bronchocentric and preservation of the underlying lung architecture. Surgical biopsy is more likely to be needed in DIP than RBILD, but is warranted if either diagnosis is suspected; however, a realistic alternative diagnosis cannot be excluded noninvasively.

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