Respiratory Bronchiolitis With Fibrosis–Interstitial Lung Disease

A New Form of Smoking-Induced Interstitial Lung Disease

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The recent pathology literature has described a new form of localized interstitial fibrosis associated with heavy cigarette smoking. This lesion has been referred to by various names, including respiratory bronchiolitis–interstitial lung disease with fibrosis, airspace enlargement with fibrosis, and smoking-related interstitial fibrosis. We have suggested that, to avoid confusion with other forms of smoking-related interstitial lung disease (ILD), the lesion be referred to as respiratory bronchiolitis with fibrosis (RBF). Most importantly, we have found that this pathologic abnormality often has a distinctive high-resolution computed tomography (HRCT) correlate, such that in many cases RBF should be diagnosable on the basis of imaging. The purpose of this short article is to suggest how RBF fits into the general category of smoking-related ILD, and particularly to compare it with two possibly related forms of accepted smoking-related ILDs: respiratory bronchiolitis–interstitial lung disease (RBILD) and desquamative interstitial pneumonia (DIP).

RESPIRATORY BRONCHIIOLITIS AND RBILD

Respiratory bronchiolitis (RB) can be identified by microscopic examination of the lungs of essentially all current cigarette smokers and many ex-smokers, and it consists of collections of pigmented macrophages (“smoker’s macrophages”) in the lumens of respiratory bronchioles and surrounding alveoli. Sometimes there is accompanying mild fibrosis of the walls of the respiratory bronchiole, more distal alveolar ducts, or surrounding alveolar walls, although historically the question of how much fibrosis has been allowed in RB as opposed to RBILD is poorly defined and certainly confused (see below). On HRCT imaging, RB is usually characterized by bronchial wall thickening and poorly defined ground glass centrilobular nodules, and sometimes by more extensive ground glass opacities, which are typically upper zonal and midzonal.

In 1987 Myers et al described 6 patients with clinical features of an ILD, including restrictive pulmonary function abnormality in 4 patients, and interstitial markings on chest radiograph but only a morphologic picture of RB on biopsy. Myers et al called this “respiratory bronchiolitis causing interstitial lung disease” and suggested that extension of the inflammation and fibrosis into the adjacent alveolar walls separated this lesion from RB. Yousem et al subsequently reported a series of 18 cases under the name “respiratory bronchiolitis-associated interstitial lung disease,” usually now referred to as RBILD. Many of their patients had a restrictive pattern of pulmonary function, and all had a decreased diffusing capacity. A total of 72% had reticular or reticulonodular opacities on plain chest radiograph. They commented that in asymptomatic RB, fibrosis is minimal, whereas it appears that they defined morphologic RBILD on the basis of extension of fibrosis into the alveolar walls, although this was not stated explicitly.

Some authors still use the extent of fibrosis as at least a partial criterion for morphologic separation of RB from RBILD. However, studies based on lung cancer resection specimens have shown that fine fibrosis in the alveolar walls around respiratory bronchioles is in fact very common in the lungs of cigarette smokers who have no clinical evidence of an ILD. Further, Wright et al found that, in fact, in most smokers fibrosis in the walls of bronchioles actually correlates with physiologic abnormalities of airflow obstruction rather than with the restrictive profile typical of most ILDs. Thus, the extent of fibrosis in or around the bronchial wall does not appear to be a useful criterion for separating RB and RBILD, and most authors make the distinction on the presence or absence of clinical features of an ILD.

The HRCT findings in RBILD are fairly similar to those of RB, but they often show a greater extent of ground glass opacities extending to the lower zones, and sometimes mild reticulation in the lower zones.

RBF AND RESPIRATORY BRONCHIIOLITIS WITH FIBROSIS–INTERSTITIAL LUNG DISEASE

The lesion we refer to as RBF was first described by Yousem, who identified it in 9 of a series of 32 patients with an ILD that was originally believed to be fibrotic nonspecific...
interstitial pneumonia. The lesion consists of sharply circumscribed areas containing a mixture of emphysema and dense, distinctively hyaline paucicellular interstitial fibrosis that often appears to radiate from the region of a respiratory bronchiole to the pleura (Figure 1, A). Smoker’s macrophages are invariably present in greater or lesser numbers in the airspaces (Figure 1, B). Fibroblast foci are rare to nonexistent.²

Katzenstein et al³ identified RBF as well as RB in 45% of extensively sampled resected lungs from cigarette smokers and termed the lesions “smoking-related interstitial fibrosis.”³ Yousem¹ found the same lesion in 4 of 30 lungs resected for lung cancer where there was no clinical question of ILD, and 2 of the cases in our series⁴ were also incidental findings in lung cancer resection specimens. Kawabata et al² described pathologic changes, termed airspace enlargement with fibrosis, some of which are the same thing (although they also appear to be including examples of centrilobular emphysema with fibrosis in the emphysematous space, which is not the same thing), in lungs from smokers; the incidence of the lesion increased with amount of smoking and was present in 21% of the heaviest smokers.² Thus, at least microscopically, some degree of localized interstitial fibrosis is present in the lungs of a significant proportion of heavy cigarette smokers.

Because the essence of RBF is a focal form of interstitial fibrosis caused by cigarette smoke, one could adopt the Katzenstein et al³ usage and label these cases as “smoking-related interstitial fibrosis,” but “smoking-related interstitial fibrosis” / “smoking-related ILD” is a term that gets used informally for a variety of forms of ILD in cigarette smokers,¹¹ including RBILD, DIP, Langerhans cell histiocytosis, and sometimes even combined pulmonary fibrosis and emphysema. Thus, to avoid confusion we think it useful to assign the lesion a different name and have proposed RBF.⁴

Why separate RBF from RB? The most important reasons are (1) as opposed to RB/RBILD, RBF is frequently mistaken, either on biopsy or HRCT, for a diffuse fibrosing interstitial pneumonia; indeed, Yousem’s original point was that this in fact was not a diffuse fibrosing lung disease; (2) RBF has a distinctive radiologic appearance on HRCT and consists of sharply circumscribed upper zonal and midzonal subpleural foci of emphysema mixed with reticulation (Figure 1, C), sometimes accompanied by areas of ground glass opacity (Figure 1, C). Of interest, the cases of RBF that we have reviewed usually do not have the centrilobular ill-defined nodules that are characteristic of RB and many cases of RBILD on HRCT.⁶ Most importantly, based on a small number of cases, the lesion is distinctive enough that it should be diagnosable on HRCT imaging alone. We make this statement with caution because it is likely that not all pathologic RBF is visible on HRCT (in a radiologic survey of heavy smokers we found the lesion on HRCT in about 5% of cases [A.C. et al, 2014]), but what does appear clear is that RBF will not look like functionally significant forms of ILD, such as usual interstitial pneumonia or nonspecific interstitial pneumonia, on HRCT.

RBILD AND RESPIRATORY BRONCHIOLITIS WITH FIBROSIS–INTERSTITIAL LUNG DISEASE

Respiratory bronchiolitis and RBILD constitute two ends of a spectrum: most patients with morphologic RB have either airflow obstruction or no functional abnormality, but there is a small subset of patients with only morphologic RB
Pathology/Clinical Entities and Functional Effects

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<tr>
<th>Probably No Effect (Usual Scenario)</th>
<th>Mild Interstitial Lung Disease (Uncommon Scenario)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory bronchiolitis</td>
<td>Respiratory bronchiolitis–interstitial lung disease</td>
</tr>
<tr>
<td>Respiratory bronchiolitis with fibrosis</td>
<td>Respiratory bronchiolitis with fibrosis–interstitial lung disease</td>
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</tbody>
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on biopsy who clinically have an ILD that is labeled RBILD (Table). We propose that exactly the same phenomenon applies to patients with morphologic or radiologic RBF; in most individuals RBF is inconsequential, but a few have clinical evidence of a mild ILD, and this disease should be called respiratory bronchiolitis with fibrosis–interstitial lung disease (RBFILD; Table).

In retrospect, it is highly likely that cases of RBF producing ILD (ie, RBFILD) were included in cases originally called RBILD. Myers et al noted that some of their cases were confused with usual interstitial pneumonia because of the presence of interstitial fibrosis around the bronchioles, implying a significant amount of fibrosis, and in fact, Figure 4 in their original paper appears to be RBF. Yousem et al found “thick fibrous septa” around the respiratory bronchioles in some of their RBILD cases, a description that fits RBF. In his more recent description Yousem suggested that some RBF patients may have signs and symptoms of an ILD, and 2 of his patients had a mixed obstructive/restrictive abnormality (ie, RBFILD). In our series, 3 patients had mild airflow obstruction, whereas 2 had airflow obstruction with evidence of restriction; however, both of these latter patients were massively obese (body mass indexes of 46 and 38, respectively), so the evidence for ILD-associated functional abnormalities is equivocal. Given the frequency of RBF morphology in cigarette smokers, other series of RBILD patients probably include patients with RBF as well.

**PROGRESSION OF RB, RBILD, RBF, AND RBFILD**

An important question is whether these lesions remain localized in a morphologic sense as well as in a functional sense. The usual belief, based mostly on pathologic findings, is that RBILD can progress to desquamative interstitial pneumonia (ie, the localized peribronchial accumulation of smoker’s macrophages in RBILD spreads to encompass more and more of the parenchyma, eventuating in disease in which large portions of the lung are filled with smoker’s macrophages, and in which there is also some amount of interstitial fibrosis and interstitial inflammation; Figure 2). Not all authors accept this scenario, and some believe that RBILD and DIP are separate entities. Further, it is not at all clear whether patients who develop DIP actually have RBILD (ie, a clinically detectable ILD) as a precursor, rather than simply having progressive florid respiratory bronchiolitis that eventually is diffuse enough and severe enough to produce functional abnormalities.

Also of interest is the fact that some cases of DIP progress to either a picture of fibrotic nonspecific interstitial pneumonia or a process that radiologically is characterized by honeycombing and resembles usual interstitial pneumonia. Overall survival in DIP ranges from about 70% to 95%. Thus, in a few patients what starts as RB can end as a significantly impairing or lethal fibrosing ILD (Figure 2).

For RBF and RBFILD there is little information about progression. In the Katzenstein et al3 series, no patients developed evidence of a diffuse fibrosing ILD, but follow-up was relatively short (mean, 16 months). Yousem reported that 2 of 9 RBF patients had progressive disease, but in fact the progression was an increase in airflow obstruction, not restriction (S. Yousem, MD, e-mail communication, February 20, 2014), and there was no information on radiologic changes over time. In our experience, based on HRCT imaging of a small number of cases, the reticulation/emphysematous foci usually appeared to be stable during several years of follow-up, there was no evidence of progressive or diffuse fibrosis, and these patients did not have worsening of clinical symptoms.

Thus, it is possible the pathology and imaging features that bring RBF/RBFILD to attention represent a morphologic and radiologic dead end (Figure 2). However, RBF cases sometimes have ground glass opacities on HRCT (Figure 1, C), which may represent areas of RB or RBILD, and it is certainly possible that, like ordinary RB/RBILD, these areas might progressively expand, ending in a picture of DIP.

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**Figure 2.** Proposed relationships of the diseases discussed in this paper. Abbreviations: DIP, desquamative interstitial pneumonia; ILD, interstitial lung disease; IP, interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; RBF, respiratory bronchiolitis with fibrosis; RBF-ILD, respiratory bronchiolitis with fibrosis–interstitial lung disease; RBILD, respiratory bronchiolitis–interstitial lung disease; UIP, usual interstitial pneumonia.
(Figure 2). These questions will require examination of a larger numbers of cases with follow-up.

References