Clinical Manifestations of Respiratory Bronchiolitis as an Incidental Finding in Surgical Lung Biopsies: A Retrospective Analysis of a Large Austrian Registry

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Abstract

Background: While respiratory bronchiolitis (RB) is a frequent histopathological finding in smoker’s lungs, RB-associated interstitial lung disease (RB-ILD) remains a rare disease. Objectives: We analyzed how the histological finding of RB was associated with clinical information in a series of 684 consecutive surgical lung biopsies. Methods: Retrospective analysis with delineation of clinical manifestations, smoking habits, pulmonary function test, and blood gas analysis in patients with RB in surgical lung biopsy. In 240 of these biopsies, RB was diagnosed, and in 146 of these cases a full clinical dataset was available. Results: The final diagnosis of these 146 patients was consistent with RB-ILD (n = 18), pulmonary Langerhans cell histiocytosis (n = 7), various ILD (n = 9), spontaneous pneumothorax (n = 43), traumatic pneumothorax (n = 5), lung cancer (n = 41), various benign lung tumors (n = 8), and chronic pulmonary effusion (n = 15). Smoking history was positive in 93% of patients, 72% revealed centrilobular emphysema in their biopsy, and 58% described dyspnea as the main symptom. Amongst these diagnoses there were significant differences in age and smoking habits, but only small distinctions in pulmonary function test and blood gas analysis. Out of the patients with RB-ILD, 17% developed lung cancer in the later course. Conclusion: RB is strongly related to smoking, emphysema, and dyspnea and frequently associated with lung cancer. RB-ILD is a rare disease that may represent a considerable risk for lung cancer. Pulmonary function testing and blood gas analysis do not differ between RB-associated diseases. The finding of RB should prompt further diagnostic workup, and in case of RB-ILD, entail regular screening for lung cancer.

Key Words
Alveolar macrophages · Lung biopsy · Respiratory bronchiolitis · Lung cancer · Histiocytosis · Interstitial lung disease

Introduction

Respiratory bronchiolitis (RB), first described in 1974 [1], is a well-recognized histopathological pattern which was initially considered to be ‘of little clinical significance’. It is characterized by the accumulation of pigmented macrophages within the respiratory bronchioles and adjacent alveoli [2]. Considered to be the anatomic correlate of...
Respiratory Bronchiolitis in Surgical Lung Biopsies

Between 1998 and 2009, histological specimens of 684 consecutive patients were obtained via open lung biopsy or video-assisted lung biopsy for diagnostic reasons. Surgical intervention was performed for routine diagnostic workup of pulmonary tissue in diffuse parenchymal lung disease (DPLD; n = 69; 10%), pneumothorax (n = 101; 15%), lung tumors including nodular lesions and hilar lymphadenopathy (n = 463; 68%), and miscellaneous causes (n = 51; 7%). The diagnosis of RB was made in 240 of these histological specimens, including 54 cases of DPLD, 74 cases of pneumothorax, 74 cases of LC, and 38 cases of miscellaneous causes. A full dataset, including smoking habits, lung function test (LFT), blood gas analysis, chest X-ray, and HR-CT prior to surgery, was available in 146 patients, including 34 patients with DPLD, 48 patients with pneumothorax, 49 patients with LC, and 15 patients with miscellaneous causes. We retrospectively reviewed these cases in the files of the Medical University of Graz. Of the 146 patients, 109 (75%) were assigned to 4 distinct groups: (1) RB-ILD (n = 18) – the diagnosis of RB-ILD was made when HR-CT scans of the lung suggested presence of ILD, histological criteria for RB were met, and other distinct DPLD had been ruled out, (2) RB associated with PLCH (RB-PLCH; n = 7), (3) RB associated with spontaneous pneumothorax (RB-SP; n = 43), and (4) RB associated with LC (RB-LC) (n = 41). We describe clinical manifestations, smoking habits, pulmonary function test, and blood gas analysis and compare anthropometrics and functional data of these 4 major patient groups. The remaining 37 patients were not eligible for statistical analysis due to their heterogeneity (fig. 1). The study was approved by the Ethics Committee of the Medical University of Graz (EK No.: 21-377 ex 09/10).

**LFT and Blood Gas Analysis**
Forced expiratory 1-second volume (FEV₁), forced vital capacity (FVC), ratio of FEV₁ to FVC (FEV₁/FVC), maximal expiratory flow at 50% of FVC (MEF50), maximal expiratory flow at 25% of FVC (MEF25), total lung capacity, residual volume, and airway resistance were determined by standard procedures. All measurements conformed to the guidelines of the European Community for Steel and Coal, and for each individual values were expressed as percentage of predicted values. Blood gas analysis was sampled from arterialized capillary blood at rest with determination of arterial oxygen (paO₂) and carbon dioxide partial pressure (paCO₂), oxygen saturation (O₂-Sat), and alveolar-arterial oxygen gradient (AaDO₂).

**Radiological Features**
For the diagnosis of RB-ILD, HR-CT scans of the lung were evaluated for ground glass opacities, central and/or peripheral wall thickening, centrilobular nodules, centrilobular emphysema, reticulation of the lower lungs, patchy areas of hypoaeration, and honeycombing.

**Histopathological Specimens**
Hematoxylin and eosin-stained sections of formalin-fixed and paraffin-embedded sections were examined. The diagnosis of RB was made when abundant pigment-laden macrophages (smokers’ macrophages) in patchy distribution were present in the lumen of respiratory bronchioles both with extension into the centrilobular lumen of alveolar spaces. The characteristic appearance is shown in figure 2.

**Statistics**
Data were analyzed using the SPSS statistical package (SPSS version 18.0; SPSS Inc., Chicago, Ill., USA). The groups were tested for statistical significance using Kruskal-Wallis ANOVA. We employed the Mann-Whitney-Wilcoxon test for comparison of 2 patient groups. Bonferroni correction was applied where multiple testing was performed. Data are given as mean ± SD. p values <0.05 were considered significant.

**Materials and Methods**
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Results

Of 240 patients with RB, 146 patients were eligible for further analysis. Of these 146 patients, 135 had a definitive smoking history (93%). In 7 cases, the smoking status was not available (1 female patient with PLCH, 1 female patient with ‘other’ DPLD, and 5 male patients with SP), and 4 patients were definitive never-smokers (2 male patients with ‘other’ DPLD, 1 female patient with ‘other’ lung tumor, and 1 female patient with ‘miscellaneous

Fig. 1. Distribution of disease entities found in association with RB. SLB = Surgical lung biopsy; PE = probe excision (via bronchoscopy or CT-guided needle aspiration).

Fig. 2. Histological findings in RB. a Macrophages in abundance in a respiratory bronchiolus (asterisk) and neighboring alveolar spaces (arrowheads). b Macrophages with typical brownish pigmentation. Hematoxylin and eosin staining. Scale bar = 100 μm.
cause’). We assigned 109 patients (75%) to 4 distinct groups: RB-ILD (n = 18), RB-PLCH (n = 7), RB-SP (n = 43), and RB-LC (n = 41; including 26 patients with pulmonary adenocarcinoma and 15 patients with squamous cell carcinoma of the lung). When comparing these 4 groups with each other, we found that patients with RB-ILD were significantly older and had significantly more pack years than patients with RB-SP. On the other hand, patients with RB-ILD were significantly younger and had significantly fewer pack years than patients with RB-LC. For further age comparison, see Table 1.

Average LFT of all 146 patients with RB were close to normal with a slight tendency towards obstruction (FEV1 74 ± 19%, FVC 79 ± 19%, and FEV1/FVC 81 ± 12%). While patients with RB-SP showed near to normal LFT after recovery, patients with RB-ILD showed a predominance of obstruction with a slight tendency towards restriction.

### Table 1. Distribution, anthropometric data, and smoking habits of patients with ‘major’ disease entities found in association with RB

<table>
<thead>
<tr>
<th>Distribution/anthropometrics</th>
<th>Diagnosis</th>
<th>M:F</th>
<th>Age, years</th>
<th>Pack years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All RB (n = 146)</td>
<td>RB-ILD (n = 18)</td>
<td>13:5</td>
<td>48 ± 11</td>
<td>30 ± 26</td>
</tr>
<tr>
<td></td>
<td>PLCH (n = 7)</td>
<td>4:3</td>
<td>38 ± 10</td>
<td>29 ± 29</td>
</tr>
<tr>
<td></td>
<td>Other (n = 9)</td>
<td>6:3</td>
<td>49 ± 4</td>
<td>19 ± 12</td>
</tr>
<tr>
<td>DPLD + RB (n = 34)</td>
<td>Spontaneous (n = 43)</td>
<td>29:14</td>
<td>31 ± 11</td>
<td>14 ± 8</td>
</tr>
<tr>
<td></td>
<td>Traumatic (n = 5)</td>
<td>5:0</td>
<td>29 ± 9</td>
<td>19 ± 17</td>
</tr>
<tr>
<td>Pneumothorax + RB (n = 48)</td>
<td>LC (n = 41)</td>
<td>26:15</td>
<td>60 ± 9</td>
<td>47 ± 30</td>
</tr>
<tr>
<td></td>
<td>Other (n = 8)</td>
<td>4:4</td>
<td>47 ± 9</td>
<td>28 ± 11</td>
</tr>
<tr>
<td>Lung tumor + RB (n = 49)</td>
<td>Miscellaneous (n = 15)</td>
<td>11:4</td>
<td>49 ± 15</td>
<td>31 ± 19</td>
</tr>
</tbody>
</table>

Age and smoking habits are given as means ± SD.

### Table 2. LFT and blood gas analysis of patients with RB and associated diseases

<table>
<thead>
<tr>
<th>LFT and BGA</th>
<th>RB-ILD (n = 18)</th>
<th>RB-SP (n = 43)</th>
<th>RB-LC (n = 41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, % predicted</td>
<td>68 ± 17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>81 ± 17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>74 ± 20</td>
<td>0.001</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>73 ± 20</td>
<td>80 ± 17</td>
<td>84 ± 19</td>
<td>0.025</td>
</tr>
<tr>
<td>FEV1/FVC, % predicted</td>
<td>84 ± 9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>89 ± 10&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>74 ± 10&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>≤0.001</td>
</tr>
<tr>
<td>MEF50, % predicted</td>
<td>63 ± 19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>83 ± 26&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>53 ± 32&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≤0.001</td>
</tr>
<tr>
<td>MEF25, % predicted</td>
<td>51 ± 27&lt;sup&gt;a&lt;/sup&gt;</td>
<td>82 ± 27&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>44 ± 21&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≤0.001</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>80 ± 21&lt;sup&gt;b&lt;/sup&gt;</td>
<td>88 ± 13&lt;sup&gt;c&lt;/sup&gt;</td>
<td>105 ± 26&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>0.002</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>101 ± 37&lt;sup&gt;b&lt;/sup&gt;</td>
<td>108 ± 35&lt;sup&gt;c&lt;/sup&gt;</td>
<td>143 ± 49&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>0.002</td>
</tr>
<tr>
<td>Rtot, kPa × s/l</td>
<td>0.19 ± 0.15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.16 ± 0.15&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.30 ± 0.28&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>≤0.001</td>
</tr>
<tr>
<td>paO&lt;sub&gt;2&lt;/sub&gt;, mm Hg</td>
<td>70 ± 12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>81 ± 16&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>75 ± 9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.058</td>
</tr>
<tr>
<td>paCO&lt;sub&gt;2&lt;/sub&gt;, mm Hg</td>
<td>38 ± 5</td>
<td>40 ± 6</td>
<td>39 ± 5</td>
<td>0.019</td>
</tr>
<tr>
<td>AaDO&lt;sub&gt;2&lt;/sub&gt;, mm Hg</td>
<td>30 ± 13&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20 ± 9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25 ± 10</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Values are given as means ± SD. In patients with RB-SP, data of LFT and BGA were obtained after pulmonary recompensation. In case of RB-ILD and RB-LC, data were obtained from the preoperative investigation closest to diagnosis. BGA = Blood gas analysis; TLC = total lung capacity; RV = residual volume; Rtot = total airway resistance.

<sup>a</sup> p values <0.05 were considered significant (Kruskal-Wallis, ANOVA); <sup>b</sup> significant difference between RB-ILD and RB-SP; <sup>c</sup> significant difference between RB-ILD and RB-LC; <sup>d</sup> significant difference between RB-SP and RB-LC.
nantly restrictive pattern with an additional aspect of small-airways obstruction with a MEF50 of 63 ± 19% predicted and a MEF25 of 51 ± 27% predicted. Whereas patients with RB-LC were more obstructive, especially in the smaller airways, with a MEF50 of 53 ± 32% predicted and a MEF25 of 44 ± 21% predicted, resembling small-airways disease. Patients with RB-ILD showed the lowest paO₂, the lowest paCO₂, and the highest AaD O₂ values in comparison to patients with RB-SP, RB-LC (table 2), and RB-PLCH (data not shown). There were no significant anthropometric, functional, and clinical differences between patients with RB-SP and patients with pneumothorax caused by trauma, and there were no significant differences between patients with relapsing and non-relapsing pneumothorax.

In the RB-ILD patients, the HR-CT scans revealed 2–6 of the following radiological features, suggesting presence of ILD. In 13 patients (72%) we found ground glass opacities, in 9 patients (50%) central and in 8 patients (44%) peripheral wall thickening, in 9 patients (50%) centrilobular nodules, in 8 patients (44%) centrilobular emphysema, in 5 patients (28%) reticulation with predominance of the lower lungs, in 4 patients (22%) patchy areas of hypoattenuation, and in 2 patients (11%) honeycombing. Honeycombing was a minor finding in both patients affected.

In terms of clinical manifestations at first presentation, 60 (41%) of 146 patients reported cough, which was associated with expectorations in 25 cases (17%). Eighty-five patients (58%) suffered from dyspnea and 71 patients (48%) from thoracic pain. Significant differences were only seen between the RB-SP and the RB-ILD group with regard to thoracic pain and dyspnea. Based on histological findings, in addition to RB, 106 of the 146 patients (73%) had a pronounced centrilobular pulmonary emphysema which was most frequently documented in the group of patients with RB-SP (table 3). The male:female ratio of the emphysema patients was 2.5:1 (76:30).
In patients with RB-ILD, long-term survival has not been described in detail. Former studies have suggested a relatively good prognosis. However, the 18 RB-ILD patients identified in our study had no favorable outcome. Six patients (33%) died within 5 years (fig. 3), 7 patients were lost to follow-up, and 5 patients are still alive. Of the 5 patients alive, 4 patients quit smoking and have since had a stable LFT, 1 patient continues smoking with a significant yearly decline in LFT.

**Discussion**

RB-ILD is histologically characterized by an intraluminal and intra-airspace accumulation of finely pigmented macrophages associated with peribronchiolar inflammation and fibrosis [1, 24–26]. Associations between RB and RB-ILD and different lung diseases, such as PLCH, SP, and LC [21, 22, 27], have been reported, and previous studies support the idea that an overlap between different smoking-related diseases is frequent [12, 16, 20]. Our data confirm that RB is nearly always associated with cigarette smoking, and that RB is strongly associated with centrilobular emphysema, SP, and PLCH which supports the hypothesis that RB may be a prerequisite for SP and PLCH, and that RB, and RB-ILD to some extent, may be a surrogate or forerunner diagnosis pointing to a higher risk of the patient to develop smoke-associated cancer subsequently (fig. 4). Causes might be similar to those described for LC and pulmonary fibrosis, a disease related to cigarette smoking likewise [28]. Of note, 3 of our patients with RB-ILD (17%) died of LC in the later course, and 2 patients died of other smoke-related cancers. In the RB-LC group, 26 (63%) patients had an adenocarcinoma and 15 (37%) patients had a squamous cell carcinoma. This is in line with a recent report [29], where RB was primarily observed in patients with adenocarcinoma, whereas RB-ILD was associated with peripheral squamous cell carcinoma.

In accordance with previous reports, the overall sex ratio showed a 2:1 male preponderance, with similar proportions in all groups. Within the 4 disease groups, 95% had a definitive smoking history ranging from 1 to 180 pack years. Our patients with RB and associated diseases demonstrated only slight impairment of their LFT – resembling small-airways disease – and rarely presented with hypoxemia. Due to its subclinical presentation, RB is usually not diagnosed until signs and symptoms of associated pulmonary diseases occur. In the 4 groups of patients with RB, we found small nonsignificant differences in anthropometric data and lung function.

In patients with RB-SP or RB-LC, diagnosis was generally triggered by clinical manifestations of pneumothorax or LC, respectively, and supported by radiological imaging. It is known from the literature that patients with PLCH almost always have RB and frequently develop pneumothorax [23], leading to diagnosis in many cases. In our population, 3 of 7 patients with PLCH had a SP prior to diagnosis. This is in contrast to patients with RB-ILD, where clinical manifestations are often subtle, X-ray of the chest is not sensitive enough, and surgical lung biopsy may not be able to distinguish RB from RB-ILD. In terms of clinical manifestations, course and outcome of RB-ILD, data are sparse and partially controversial, with only a few case series and reviews reported. The most important clinical manifestations reported in RB-ILD are dry cough, shortness of breath, exertional dyspnea, and...
weight loss, eventually dyspnea at rest and rarely thoracic pain. In our RB-ILD patients, the leading symptoms, sole or combined, were dyspnea (56%) and, more frequent than in any other disease group, cough (56%), sputum production (44%), and night sweats (11%). Less pronounced symptoms were thoracic pain (22%) and fever (6%). Hemothysis and velcro rales on auscultation were rarely present, and clubbing, reported with an incidence of 12.5–33% in patients with RB-ILD [21, 30], was only seen in 2 of our cases (11%).

Pulmonary function testing and blood gas analysis were not helpful to differentiate diseases associated with RB. Patients with RB-ILD and RB-LC showed functional signs of small-airways disease characterized by a marked reduction of the MEF50 and MEF25. Histologically, a predominantly centrilobular emphysema occurred significantly more often in patients with RB-SP and in those with RB-LC, representing the majority of the analyzed patients. Patients with RB-ILD additionally showed a mild restrictive ventilatory pattern, and blood gas analysis demonstrated an augmented AaDO2 and a decrease in paO2 and paCO2 as would be expected in DPLD. Some patients showed combined ventilatory impairment, whereas others presented only with a mild decrease in diffusing capacity of the lung for carbon monoxide. In a few patients, only residual lung volumes were increased, indicating air trapping beyond the obstructed bronchiole, while other patients had a normal pulmonary function test.

Our study has several limitations. The retrospective nature of our study with clinical, physiological, radiological, and gas exchange data, which were not acquired for study purposes but as a clinical routine, and the small number of cases limit the value of the statistical analysis and the strength of the conclusions. We introduced a potential selection bias by enrolling only patients, in whom the disease had been confirmed histologically via surgical lung biopsy. As only 16% of all patients with LC had histologically reported RB, one may speculate that RB was not always worth mentioning, resulting in underreporting. A further limitation is the general difficulty that associations may not be interpreted as causal relationships. The strongest causal factor behind both RB and the associated diseases was certainly cigarette smoking.

**Conclusion**

RB is caused by cigarette smoke and is related to lung emphysema, LC, PLCH, SP, and ILD. The diagnosis of RB-ILD is essentially clinical/radiological, requiring the presence of a variable combination of symptoms, clinical signs, and abnormal findings on chest radiography or HR-CT. Since RB and RB-ILD are strongly associated with LC, incidental findings should induce close follow-up observation and a very strong recommendation to stop smoking.

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**Financial Disclosure and Conflicts of Interest**

The authors have no conflicts of interest to disclose.

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