ABSTRACT: Respiratory bronchiolitis (RB) is defined by the accumulation of pigmented macrophages in the lumen and wall of respiratory and membranous bronchioles of smokers. The aim of this study was to determine whether spontaneous pneumothorax was associated with a high prevalence of RB.

Seventy-nine consecutive patients who underwent a surgical procedure (thoracotomy or thoracoscopy) for recurrence or persistence of primary spontaneous pneumothorax despite thoracic drainage were studied retrospectively.

RB was found in 70 of 79 (88.6%) smokers operated for spontaneous pneumothorax. Associated interstitial pathological abnormalities were present in 53 of 79 cases (67.1%). In nine patients, the pathological lesions were severe and resembled desquamative interstitial pneumonia. Emphysematous lesions were present in about one-third of the patients.

Although the possible pathophysiological consequences of respiratory bronchiolitis remain speculative, this study demonstrates the high prevalence of this pathological abnormality in patients with pneumothorax requiring surgical treatment.


Patients and methods

Patients

One-hundred and eighteen patients underwent a surgical procedure for primary spontaneous pneumothorax, including a pulmonary biopsy, between 1978 and 1996 in the authors’ hospital. Primary pneumothorax was defined by the exclusion of aetiological factors [2]. Fifteen patients were excluded because the pulmonary biopsy was too small to allow the study of bronchioles, 24 patients were nonsmokers and 79 patients were smokers and retained for the study. Indications for surgery were recurrent pneumothorax (n=44), persistent air leak after 8 days of chest drainage or early recurrence after removal of the chest tube (n=27), and/or prior contralateral pneumothorax (n=8).

Surgery

Fifty patients underwent open surgical procedures and 29 videothorascopic procedures. The lungs were thoroughly inspected for blebs, bullae or air leaks, which were removed, together with the underlying peripheral part of the lung parenchyma (about 1 cm thick), and conserved for histological examination. Pleurodesis was obtained by parietal pleural abrasion using dry gauze (n=26), apical pleurectomy (n=66), talc insufflation (n=7) and/or biological glue (n=21).

Histological examination

The specimens were embedded in paraffin. The blocks were cut in 1–2 µm sections and stained with haematoxylin-phloxine-saffron for light microscopy. Perls’s staining was used when the type of deposited pigments (haemosiderin or tobacco-associated pigments) was in doubt. From
each specimen the following histological features were assessed: number of respiratory bronchioles present in the sample, RB, inflammatory cell infiltration or fibrotic changes to the airway wall and interstitial spaces, pigment deposition and concomitant emphysematous lesions.

RB was defined [3] by the accumulation of pigmented macrophages in the lumen and wall of respiratory bronchioles (obligatory), and in neighbouring alveolar ducts and alveoli, associated with submucosal and peribronchiolar infiltration by inflammatory cells in adjacent bronchiolar walls. Severity of RB was graded according to the extent of pigmented macrophage deposition around the respiratory bronchus: grade 1 was defined by the accumulation of pigmented macrophages limited to the lumen and wall of respiratory and membranous bronchioles (at least one bronchiole involved) and to a single-layer ring of peribronchiolar alveoli; grade 2 was defined as the extent of the deposition of tan-brown macrophages in the adjacent alveolar ducts and alveoli; grade 3 was defined as a massive deposition of pigmented macrophages in the peribronchiolar area, with RB not involving all the bronchioles of the sample; and grade 4 was defined as a massive involvement of bronchiolar and alveolar lumen in the whole sample. Concomitant interstitial lung disease (ILD) was defined by an excess of connective tissue in the interstitium and/or interstitial inflammatory cell infiltration [4, 5]. The concomitant presence of emphysema was also investigated, and it was further classified into centrilobular, panlobular and localized (paraseptal) emphysema.

**Results**

**Patient characteristics**

The patients were 63 males and 16 females, aged 40±12 yrs (range 17–71). Mean height was 173±9 cm (152–197), weight 62±11 kg (42–97) and body mass index 20.4±2.5 kg·m⁻² (15.6–28). All were smokers with a mean smoking history of 13.8±12.6 pack-yrs (1–60). α₁-Antitrypsin level, surprisingly, a marked intimal fibrosis of the small pulmonary arterioles was frequently noted (39%).

**Perioperative findings**

Perioperative macroscopic examination of the lung revealed active air leak in 11 cases, subpleural bullae in 74 cases and pleural adhesions in 22 cases.

**Histological findings of lung tissues**

RB was found in 70 of 79 smokers operated for spontaneous pneumothorax (88.6%). The grading of RB is shown in table 1. Histological RB-associated ILD was present in 53 of 79 cases (67.1%). The main interstitial abnormality associated with RB was a thickening of the interstitial structures, consisting of an excess of connective tissue. Inflammatory cell infiltration of the alveolar and interlobular septa, the peribronchiolar zone and the visceral pleura was also frequent. In nine patients, marked interstitial abnormalities were associated with massive deposition of pigmented macrophages involving all bronchiolar and alveolar lumens in the sample (RB grade 4); the pathological lesions in these patients resembled desquamative interstitial pneumonia. A mild thickening of the interstitial spaces without inflammatory infiltration was also noted in two patients without RB. Non-tobacco pigment deposition was markedly less frequent than tobacco-associated pigments (table 1). Emphysematous lesions were present in about one-third of the patients, but distinguishing between different classes of emphysematous lesions was difficult because of the small size of many surgical samples. Surprisingly, a marked intimal fibrosis of the small pulmonary arterioles was frequently noted (39%).

**Discussion**

Although RB may be a common finding in healthy smokers, its precise prevalence is not known. In the present study RB was found in nearly 90% of lung biopsy specimens from smokers requiring surgical pleurodesis for spontaneous pneumothorax. Since the specimens for histological examinations consisted of the area of lung parenchyma adjacent to the resected lesions and RB occurs in an irregular distribution [3] this prevalence may even be underestimated.

In a subset of patients, RB is associated with ILD and manifests with dyspnoea, pulmonary function and radiological abnormalities [4–6]. In the present study, RB was frequently associated with thickening of the interstitial spaces, together with inflammatory cell infiltration of the alveolar and interlobular septa and the peribronchiolar zone. In these patients with ILD, RB lesions were more pronounced, as reported previously [5, 7], and resembled

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### Table 1. – Histological findings of lung tissues

<table>
<thead>
<tr>
<th>Patients n (%)</th>
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<tbody>
<tr>
<td>Number of bronchioles per sample</td>
</tr>
<tr>
<td>Respiratory bronchiolitis</td>
</tr>
<tr>
<td>Grade 1</td>
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<tr>
<td>Grade 2</td>
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<td>Grade 3</td>
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<td>Grade 4</td>
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<tr>
<td>Overall</td>
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<tr>
<td>Interstitial abnormalities</td>
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<tr>
<td>Fibrosis</td>
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<tr>
<td>Inflammatory cell infiltration</td>
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<tr>
<td>Emphysema</td>
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<tr>
<td>Lookpolyphalous</td>
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<tr>
<td>Haemosiderin</td>
</tr>
<tr>
<td>Bullae</td>
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<tr>
<td>Tobacco-associated pigments</td>
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<tr>
<td>Overall</td>
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<tr>
<td>Arteriolar intimal fibrosis</td>
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</table>

†: Expressed as per cent of positive cases of respiratory bronchiolitis.
desquamative interstitial pneumonia, an entity distinct from RB. Accumulation of intra-alveolar macrophages and mild interstitial thickening occur in both conditions, but in RB the process is patchy and follows a peribronchiolar distribution [8].

Although a high prevalence of RB in patients with spontaneous pneumothorax has been shown by the present study, its pathophysiological significance remains to be clarified. Peripheral airway lesions such as RB may be the precursor of more severe anatomical lesions such as centriacinar emphysema [9]. The tobacco-induced chronic inflammatory reaction may spread centrifugally from the small airways to the adjacent parenchyma and lead to progressive destruction of peribronchiolar alveoli [10]. Some support for this concept has come from the demonstration of a relationship between bronchiolar disease and centriacinar emphysema in previous pathological studies [6, 9, 11, 12]. In addition, physiological studies have shown a link between tobacco-associated bronchiolar disease such as RB and functional abnormalities of the small airways [13, 14]. A similar mechanism may be involved in the pathogenesis of subpleural bullae and blebs in smokers, lesions frequently associated with idiopathic spontaneous pneumothorax [15]. Whether tobacco-induced pathological changes in the small airways including RB might contribute to the development of focal emphysema with consequent formation of bullae, thus predisposing to spontaneous pneumothorax, remains to be studied.

Although the possible pathophysiological consequences of respiratory bronchiolitis remain speculative, this study demonstrates the high prevalence of this pathological abnormality in patients with pneumothorax requiring surgical treatment.

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