Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

Respiratory bronchiolitis and lung carcinoma

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ARTICLE INFO

Article history:
Received 16 February 2012
Received in revised form
19 March 2013
Accepted 22 March 2013
Available online 7 June 2013

Keywords:
Smoking
Respiratory bronchiolitis
Bronchiolocentric fibrosis
Smoking-related interstitial fibrosis
Squamous cell carcinoma

ABSTRACT

Background: Cigarette smoking is the primary causative factor for lung carcinoma and respiratory bronchiolitis (RB), particularly RB-associated interstitial lung disease (RB-ILD). However, the link between lung cancer and RB/RB-ILD remains undefined. We examined whether pathological fibrosis lesions exist simultaneously in patients with lung carcinoma because the fibrous lesions could be precancerous.

Methods: Clinical, radiological, and pathological features were consecutively evaluated in 67 current smokers, 22 ex-smokers, and 35 nonsmokers who underwent surgical resection for lung carcinoma. The presence of interstitial changes was evaluated by high-resolution computed tomography (HRCT). The pathological examination focused on RB, RB with fibrosis, and coexistent interstitial changes.

Results: RB with fibrosis was observed in 13/67 current smokers with centrilobular nodular and/or patchy ground-glass opacities patterns or emphysema on HRCT. RB without fibrosis was observed in 12/67 current smokers with a centrilobular pattern, emphysema, or a normal pattern on HRCT. The Brinkman smoking index was significantly higher in the RB with fibrosis group (1278±133) than in the RB without fibrosis group (791±131). No RB with/without fibrosis features were noted in nonsmokers or ex-smokers. Squamous cell carcinoma was observed in 11/13 patients with RB with fibrosis, whereas adenocarcinoma was observed in 7/12 patients with RB without fibrosis.

Conclusions: Squamous cell carcinoma located in peripheral areas was primarily observed in patients with RB with fibrosis, whereas adenocarcinoma was primarily observed in patients with RB without fibrosis. Interstitial fibrosis with RB caused by continuous heavy cigarette smoking may increase the risk of developing squamous cell carcinoma.

1. Introduction

Cigarette smoking is the primary causative factor for respiratory bronchiolitis (RB), which is characterized by inflammation of respiratory and terminal bronchioles [1]. Pathological RB is a common incidental finding in the lungs of cigarette smokers. Although patients with RB are generally asymptomatic with minimal small airway dysfunction, RB could often be associated

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http://dx.doi.org/10.1016/j.resinv.2013.03.003

with interstitial lung changes that present with pulmonary symptoms such as cough and sputum, decreased pulmonary function, and chest imaging abnormalities. This condition was previously described as respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) [2,3]. High-resolution computed tomography (HRCT) in RB-ILD reveals peripherally distributed, diffuse centrilobular, nodular, or patchy ground-glass opacities (GGOs), although no appreciable honeycombing is observed [4,5].

Idiopathic pulmonary fibrosis (IPF) is frequently associated with lung carcinoma. The mortality rate of patients with IPF complicated by lung carcinoma is higher than that of patients with IPF without lung carcinoma [6–9]. In patients with IPF and lung carcinoma, alveolar epithelial injury and cytokines activated in response to chronic inflammation may trigger the occurrence of lung carcinoma. Epidemiological studies revealed that cigarette smoking and environmental exposure to toxic substances are common risk factors for IPF and lung carcinoma. Although RB-ILD is defined as a smoking-related disease [2–5], no studies—excluding a few case reports [10]—have been conducted regarding the occurrence of lung carcinoma in patients with RB-ILD. Because such patients usually have mild symptoms and a favorable prognosis, most of them may be overlooked.

In contrast, mild degrees of alveolar wall fibrosis and focal subpleural fibrosis can be present in nearly 50% of patients with RB [11]. Therefore, most authors accept that mild alveolar wall fibrosis in certain cases of RB as well as RB-ILD extends away from the respiratory bronchioles [12]. However, some patients with RB lack pathological fibrosis findings. In the present study, we focused on the differences between RB with fibrosis and RB without fibrosis in the development of lung cancer in patients who underwent surgical resection to treat lung carcinoma.

2. Materials and methods

2.1. Subjects

The study consisted of 124 consecutive patients who underwent surgical resection to treat lung carcinoma between 1998 and 2005 in Japan Railway Tokyo General Hospital. The evaluation included clinical history, physical examination, pulmonary function, preoperative chest radiography and HRCT findings, and pathological findings in the lung specimen. Smoking history was recorded by the patients and confirmed by their relatives or individuals accompanying the patients to the examination. Current smokers were defined as those who had smoked within the previous 6 months. The study protocol was approved by the Research Ethics Committee of Japan Railway Tokyo General Hospital, and all patients provided informed consent prior to initiation of the study.

2.2. HRCT

To validate the presence of characteristic HRCT findings of subjects, namely centrilobular nodular (CN) shadows, GGOs, emphysematous changes, and interstitial changes [13,14], all images were analyzed by 2 pulmonologists independently (Y.Y and C.K).

2.3. Pathology

The lung carcinoma lesion and a region macroscopically distant from the lung carcinoma were histopathologically examined in each patient. The features related to the radiological findings were primarily evaluated because several pathological features are usually found in the lungs of smokers. The pathological findings were classified as follows: no (or minimal) pathological abnormalities, anthracosis or bronchiolocentric fibrosis without RB features (BCF), usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), smoking-related interstitial fibrosis (SRIF) appearing as collagen-type fibrosis according to Katzenstein [15], RB without fibrosis, and RB with fibrosis. Although airspace enlargement with fibrosis, as named by Kawabata [16], is similar to SRIF, the term SRIF, which reflects smoking-related lung changes more comprehensively, is applied in this study.

Characteristic RB was defined as patchy changes with a bronchiolocentric distribution, pigmented macrophages in the lumina of respiratory bronchioles, alveolar ducts, and alveolar wall fibrosis extending away from the respiratory bronchioles [1–3,11,12,17].

RB-ILD is one of the clinicopathological patterns in patients with idiopathic interstitial pneumonias, having both radiological symptoms and some degree of respiratory symptoms according to the ATS/ERS classification in 2002 [18]. Therefore, the term RB-ILD should be strictly used in the case of remarkable radiological findings and clinical interstitial pneumonitis. However, some degree of pathological interstitial fibrosis could be found in patients with RB without clinicoradiological findings. In this study, these features were also described as RB with fibrosis.

2.4. Statistics

The results are expressed as means ± standard errors. Proportions were compared using the Chi-square test. The Mann–Whitney U-test and Fisher's exact test were used to compare the Brinkman smoking index (BI) and incidence of associated lung carcinoma cell type between 2 groups of patients. P values less than 0.05 were considered statistically significant.

3. Results

According to smoking status, the subjects included 35 nonsmokers, 22 ex-smokers, and 67 current smokers. All ex-smokers in this study had quit smoking more than 3 years previously.

3.1. Radiological evaluation

Among the 67 current smokers, 49 (73%) had abnormal HRCT findings, whereas 18 (27%) had no (or minimal) abnormal HRCT findings (designated as radiologically normal). Seven patients had UIP or NSIP-like appearances (designated as the fibrous pattern). Fifteen patients had predominant