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A clinicopathological study of surgically resected lung cancer in patients with usual interstitial pneumonia

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ABSTRACT

Background: The clinicopathological characteristics of lung cancer with concomitant usual interstitial pneumonia (UIP) are insufficiently understood. This study aimed to elucidate a characteristic pathological feature of lung cancer that develops in patients with UIP, with a focus on the location of its onset.
Methods: We reviewed surgically obtained specimens, including 547 tumors from 526 patients who underwent lobectomy for lung cancer. Surveyed patients were classified into three groups: patients with UIP (UIP group), patients with lung pathology other than UIP (non-UIP group), and patients without any associated lung pathology (normal group). The histology as well as the lobe and location of the onset of lung cancer were compared among these groups. The peripheral location was subdivided into subpleural, inner and tumor involved centrally secondary to extension.
Results: The UIP group comprised 82 patients (male, 71 [87%]; mean age, 71 years; smoking rate, 94%), the non-UIP group comprised 334 patients (male, 267 [80%]; mean age, 69 years; smoking rate, 81%), and the normal group comprised 110 patients (male, 33 [30%]; mean age, 63; smoking rate, 29%). No statistical differences were noted in sex, mean age, or smoking index between the UIP and non-UIP groups. Compared with the non-UIP group, the frequency of squamous cell carcinoma (63% vs. 32%), lower lobe origin (76% vs. 32%), and subpleural location (24% vs. 5%) were significantly higher in the UIP group.
Conclusions: Lung cancers in patients with UIP show a predilection for the subpleural region, where UIP is also thought to originate.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a severe interstitial lung disease with unknown cause, pathologically presenting with usual interstitial pneumonia (UIP) [1]. IPF/UIP often coexists with lung cancer and emphysema, all of which are more prevalent in males who are heavy smokers [1–3]. IPF and lung cancer are individually associated with poor clinical outcomes [4,5]. Acute exacerbation of IPF can occur during treatment for cancer and worsens prognosis [6,7]. Lung cancer with concomitant IPF is also highly prevalent in heavy smokers, suggesting the significant impact of smoking on carcinogenesis in these comorbid disorders. However, a previous cohort study reported that the presence of IPF but not smoking history is an independent risk factor of lung cancer development [8]. Thus, consensus on the predisposing factor for lung cancer with concomitant IPF has not been achieved.

Abbreviations: IPF, Idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia; ATS, American Thoracic Society; ERS, European Respiratory Society; IIPs, idiopathic interstitial pneumonias; NSIP, nonspecific interstitial pneumonia; DIP, desquamative interstitial pneumonia; CLE, centrilobular emphysema; AEF, airspace enlargement with fibrosis; CPFE, combined pulmonary fibrosis and emphysema; SD, standard deviation; VC, volume capacity; WHO, World Health Organization.

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Lung cancer with concomitant IPF mainly consists of squamous cell subtype and is predominantly located at the lower lobe and peripheral location compared with lung cancer without IPF [9–13]. Alveolar epithelial proliferation and/or metamorphosis in the subpleural regions where UIP arises was previously reported to be the possible cause of lung cancer development [14–16]. These findings suggest that lung cancer and IPF may likely develop in the lower lobe and subpleural regions. However, reports on concomitant lung cancer and IPF according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus classification for idiopathic interstitial pneumonias (IIPs) that established standard classification of IIPs including IPF/UIP are not available [17].

Given the hypothesis that lung cancer has a predilection of development in subpleural regions in the lower lobe where UIP arises, we investigated the clinicopathological features of case patients based on the ATS/ERS consensus classification.

2. Materials and methods

2.1. Patients

We reviewed the pathological features of 526 patients (male, 371 [71%]; median age, 68 years) who underwent lobectomy or more extensive resection for primary lung cancer at the Saitama Prefectural Cardiovascular and Respiratory Center between 2003 and 2007.

2.2. Methods

Clinical records with regard to sex, age, smoking rate, smoking index, resection lobe, and pathology of all patients were available. This retrospective study was approved by the ethical committee at our hospital where this work was performed, and patient consent was not required (April 22, 2008).

We examined the resected lungs macro- and microscopically to determine the presence or absence of UIP, nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), centrilobular emphysema (CLE), bulla, airspace enlargement with fibrosis (AEF) [18], and pathological findings in pneumoconioses, such as macroscopic and histological silicotic nodules, mixed dust fibrosis, dust macule, and coal macule. The criteria for UIP, NSIP, and DIP were based on the ATS/ERS consensus classification [17]. The histological classification of lung cancer was based on the World Health Organization (WHO) criteria [19]. Patients with carcinoid tumors, adenoid cystic carcinoma, and mucoepidermoid carcinoma were excluded. Diagnosis of double cancers was based on different histologies or morphologies and/or different immunostainings when similar histological features, such as in adenocarcinoma, were present.

2.2.1. Classification of patient lungs

We classified the resected lungs into three groups as follows (Supplementary Fig. 1).

1) UIP group: Cases with macroscopically visible and histologically confirmed UIP, including combined pulmonary fibrosis and emphysema (CPFE) [20]. This group also included UIP cases with fibrosis less than 1 cm in depth (histological UIP subgroup), many of which were not clinically diagnosed as IPF (see Table 1a, Fig 1a) [21], and cases of diffuse UIP with fibrosis more than 1 cm in depth from the pleura (diffuse UIP subgroup).
2) Non-UIP group: Cases with macroscopically or microscopically visible abnormal lung lesions other than UIP as described above.
3) Normal group: Cases with normal gross and histologic findings other than carcinoma.

2.2.2. Location of lung cancer

We also divided the cases according to the primary location of the tumor as follows: 1) central type: the center of the tumor corresponds to the segmental or larger bronchus and 2) peripheral type: the center of the tumor is distal to the subsegmental bronchus. The peripheral type was further subdivided into the following: 1) subpleural: the tumor was widely attached to the visceral pleura (semispheric or zonal in shape, Fig 1b, c); 2) inner lung: the center of the tumor was separate from the pleura with/without some encroachment on the pleura (Fig 1d, e); and 3) tumors that involved the central region secondarily by direct extension from the periphery.

2.3. Statistical analysis

Values are presented as percentages or medians with interquartile ranges. Differences and trends among the groups were analyzed using Fisher's exact test, Mann-Whitney *U* test, Kruskal-Wallis test, and the Cochran–Armitage test. A p value < 0.05 was considered significant. All subsequent statistical analyses were performed using EZR software [22]. Total numbers of tumors for histological type, lobe distribution, and location include the double tumors.

3. Results

3.1. Comparison of clinicopathological features between UIP, non-UIP, and normal groups

The UIP, non-UIP, and normal groups comprised of 82 (male; 71 [86.6%]; mean age, 71; smoking rate 94%), 334 (male, 267 [80.0%]; mean age; 69, smoking rate 81%), and 110 patients (male, 33 [30.0%]; mean age, 63; smoking rate, 26%), respectively (Table 1a). The UIP group included two cases each of asbestosis and collagen-related diseases (Supplementary Table 1), and the rest were idiopathic in nature. Meanwhile, the non-UIP group consisted of two NSIP cases, two sarcoidosis, and one pulmonary alveolar proteinosis, but no case of DIP. AEF frequency between the UIP and non-UIP group was statistically different; however, no difference was observed in terms of CLE, bullae, and pathological findings in pneumoconiosis. No difference with respect to sex, age, and smoking index was noted between the UIP and non-UIP groups. However, the normal group showed statistical differences of sex, age, and smoking index compared with the former two groups.

Double primary lung cancers, including 11 tumor nodules within the same lobe, were observed in 21 cases (4 in UIP group, 14 in non-UIP group, and 3 in normal group). Therefore, subsequent analysis for histological type, lobe distribution, and location was conducted in 547 tumors. Histologically, 305 adenocarcinomas, 179 squamous cell carcinomas, 30 large cell carcinomas, 14 pleomorphic carcinomas, 13 adenosquamous carcinomas, and 6 small cell carcinomas were noted.

The frequency of squamous cell carcinoma and peripheral subpleural location decreased in the following order: UIP group, non-UIP group, and normal group. The frequency of lower lobe distribution was the highest in the UIP group, followed by the normal group, and the lowest in the non-UIP group (Supplementary Fig. 2). A total of 83% of cases in the normal group had adenocarcinoma, and none had a subpleural location.

A total of 21 cancers in the UIP group and 16 cancers in the non-UIP group had a subpleural location (Table 1b). No double primary lung cancers were noted. Squamous cell carcinomas (66.7% vs. 12.5%) and lower lobe distribution (95.2% vs. 31.2%) were more prevalent in the UIP group than in the non-UIP group. With regard to lesions suspected to have developed into subpleural cancer, the