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Lung Cancer in Chronic Hypersensitivity Pneumonitis

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Key Words
Hypersensitivity pneumonitis · Idiopathic pulmonary fibrosis · Lung cancer

Abstract
Background: So far, the association of lung cancer with chronic hypersensitivity pneumonitis (CHP) has not been studied. ***Objective:*** We examined the prevalence and revealed clinical features of lung cancer in CHP. ***Methods:*** We retrospectively reviewed the medical records from 1994 through 2005 and identified 11 patients (15 lesions) with lung cancer among 104 patients with CHP. Their clinical features and histopathological findings were analyzed. ***Results:*** Ten men and 1 woman with a median age of 68.9 years were included. All patients had a smoking history. The most prevalent histopathological type of lung cancer was squamous cell carcinoma (53%), and all tumors were located in the peripheral region of the lung. Four patients suffered from lung cancer after the diagnosis of CHP and 1 patient had lung cancer before the diagnosis of CHP. The histological pattern of CHP showed a predominantly usual interstitial pneumonia-like lesion. Tumors were located adjacent to honeycombing in 7 (47%) of 15 lesions, bullae in 4 (27%) lesions, and relatively normal lung in 4 lesions. ***Conclusions:*** Since the prevalence of lung cancer in CHP seems to be high (10.6%) as seen in idiopathic pulmonary fibrosis, physicians should be aware of the possible complication of lung cancer in CHP.

Introduction

Hypersensitivity pneumonitis (HP) is an immunologically induced lung disease caused by inhalation of a variety of environmental agents [1]. The clinical features of chronic HP (CHP) including subjective complaints of cough and dyspnea on exertion, imaging and pulmonary function abnormalities, and poor prognosis seem to be similar to idiopathic pulmonary fibrosis (IPF) [2].

Lung cancer has been identified with increased frequency (10–15%) in advanced IPF [3, 4]. In previous literature, lung cancer associated with IPF located frequently in the lower peripheral lung lobes, where the fibrosis was prominent [5–8]. From a histopathological point of view, squamous cell carcinoma was reported to be dominant in the IPF-associated lung cancer [9, 10]. CHP is postulated to be another risk factor for lung cancer since the histological fibrotic features in CHP mimic those in IPF. However, the prevalence of lung cancer in CHP has not yet been reported. We examined the prevalence and revealed clinical features of lung cancer in CHP.

Materials and Methods

Subjects

A computer-aided search was conducted to retrospectively identify all adults (>18 years old) seen at our hospital during an 11-year period from 1994 to 2005 who suffered from CHP and/or lung cancer. Among 104 patients with CHP, we identified 11 pa-

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Table 1. Patient characteristics

Case	Sex	Age at diagnosis of			Smoking	BI	Occupation
		lung cancer[a]	CHP	IPF			
1	M	71, 73	72	71[b]	S	1,800	tailor (kimono)
2	M	66	67	66[b]	S	1,200	leather worker
3	M	66	66[b]	–	Ex	2,180	shoemaker
4	M	67	67[b]	–	S	470	janitor
5	F	68	60	–	Ex	100	homemaker
6	M	83	73	–	Ex	600	sales assistant of furniture
7	M	70, 74	77	70[b]	Ex	1,000	book dealer
8	M	70, 75	77	–	Ex	1,020	pub keeper
9	M	70	69	63	Ex	920	researcher
10	M	65	67	65[b]	Ex	2,400	mail officer
11	M	62, 66	62	60	S	1,760	advertising agent

S = Current smoker; Ex = ex-smoker; BI = Brinkman index (number of cigarettes per day multiplied by years).
[a] Cases 1, 7, 8 and 11: patients suffered twice from lung cancer. [b] Simultaneously diagnosed as lung cancer.

Table 2. Causative antigens and immunological findings in CHP

Case	Type of CHP	Causative antigens	Specific antibody	LST	Provocation test
1	BRHP	next to bird shop; feather duvet; small birds	–	+	+
2	BRHP	many pigeons; silky fowl; pigeons	–	+	+
3	BRHP	parakeet; feather duvet	+	–	+
4	BRHP	unknown	+	+	+
5	BRHP	many pigeons	+	+	+
6	BRHP	parakeet	–	+	+
7	BRHP	stuffed pheasant	–	+	+
8	BRHP	parakeet	+	+	+
9	BRHP	wild birds	+	+	+
10	SHP	*Trichosporon asahii*[a]	+	+	+
11	SHP	*Trichosporon asahii*	+	ND	+

SHP = Summer-type hypersensitivity pneumonitis; LST = lymphocyte stimulation test; ND = not done.
[a] Mold in house.

tients (10.6%) who suffered from lung cancer as well as CHP. This study conformed to the Declaration of Helsinki and was approved by the institutional review board.

Diagnostic Criteria of CHP

The diagnostic criteria for CHP was 3 or more of the following (including 5, either 2 or 3, and either 1 or 6): (1) reproduction of symptoms of HP by an environmental provocation or laboratory-controlled inhalation of the causative antigen; (2) evidence of pulmonary fibrosis with or without granulomas; (3) honeycombing on computed tomography scans; (4) progressive deterioration of a restrictive impairment on pulmonary function over 1 year; (5) over 6 months' duration of respiratory symptoms related to HP, or (6) antibodies and/or lymphocyte proliferation to the presumed antigen [2].

Immunological Examinations

Specific antibodies in sera and BAL fluids were measured by an enzyme-linked immunosorbent assay [11]. An antigen-induced lymphocyte proliferation test using peripheral lympho-

Table 3. Clinical and pathological features in lung cancer

Case	Histopathological diagnosis of lung cancer	Clinical staging	Treatment	Cause of death	Survival months	Location of cancer	Background pathological condition
1	SCC U/D	IB IV	Sur BSC	lung cancer	25	LUL RLL	normal lung honeycombing
2	SCLC + Ad	IIIA	Sur, Ch	lung cancer	20	RLL	bullae
3	SCC	IIIA	Ch	lung cancer	24	RLL	bullae
4	SCLC + Lar	IIB	Sur, Ch	lung cancer	17	RLL	honeycombing
5	SCC	IB	RT	lung cancer	24	RML	normal lung
6	SCC	IV	BSC	lung cancer	9	LUL	bullae
7	SCC SCC	IA IA	Sur Sur	CHP	130	LLL RUL	honeycombing normal lung
8	Ad SCC	IIIB IIIA	Ch, RT BSC	lung cancer	109	LUL RUL	bullae normal lung
9	Ad	IV	BSC	lung cancer	2	LLL	honeycombing
10	Ad	IA	Sur	CHP	57	RLL	honeycombing
11	SCC + SCLC Ad	IB 1B	Sur, Ch BSC	lung cancer	63	LUL RUL	honeycombing honeycombing

SCC = Squamous cell carcinoma; U/D = undifferentiated lung cancer; Ad = adenocarcinoma; SCLC + Ad = combined small cell cancer and adenocarcinoma; SCLC + Lar = combined small cell cancer with large cell carcinoma; SCC + SCLC = squamous cell carcinoma with small cell cancer; Sur = surgery; Ch = chemotherapy; RT = radiation therapy; BSC = best supportive care; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; LLL = left lower lobe; RUL = right upper lobe.

cytes and bronchoalveolar lymphocytes [11, 12] and a laboratory-controlled inhalation test using pigeon dropping extracts were performed as previously reported [13].

Imaging

Chest radiograph and high-resolution computed tomography at the time of the diagnosis of lung cancer were retrospectively interpreted by two pulmonary specialists (N.I., Y.M.) without knowledge of the patient's clinical course. The primary sites of lung cancer were determined by bronchoscopic examination, if available, or high-resolution computed tomography. Cancers arising in the major bronchus up to the segmental bronchus were classified as central type, and those arising distal to the segmental bronchus were classified as peripheral type.

Histopathological Findings

Histopathological examinations were blindly interpreted by two pulmonary pathologists (H.K., T.T.) without knowledge of the patient's clinical findings. When the interpretations differed between the two pathologists, the final decision was reached by consensus. Histological types of lung cancer were classified according to the World Health Organization histological classification. The chronic inflammatory and fibrotic lesions were classified according to the ATS/ERS international consensus classification as usual interstitial pneumonia (UIP)-like, nonspecific interstitial pneumonia-like, and bronchiolitis obliterans organizing pneumonia-like lesions based on the quality of fibrotic changes including the loose and dense fibrosis, and the temporal appearance [14].

Results

Characteristics of 11 patients with lung cancer and CHP were summarized in table 1. Ten men and 1 woman with a median age of 68.9 years (range: 62–83 years) at the initial diagnosis of lung cancer were included. All 11 patients had a smoking history. Six out of the 11 patients (55%) were misdiagnosed as having IPF before having been referred to our hospital. Four of the 11 patients (cases 5, 6, 9 and 11) suffered from lung cancer after the diagnosis of CHP (or misdiagnosed as IPF); 1 patient (case 8) had lung cancer before the diagnosis of CHP, and the remaining 6 patients were diagnosed as having lung cancer and CHP (or misdiagnosed as IPF) simultaneously.

In the 104 patients with CHP, 93 patients with bird-related HP (BRHP) and 11 patients with summer-type HP were included. Among the 11 patients with CHP and lung cancer, 9 patients were diagnosed as BRHP and the remaining 2 patients as summer-type HP. The causative antigens of CHP and immunological findings are listed in table 2. In case 4, the patient refused to give detailed information about his work environment. The histological pattern of CHP was analyzed using resected lungs

with lung cancer (cases 1, 2, 4, 7, 10 and 11) or postmortem lungs (case 9), showing predominantly UIP-like lesions in all examined patients. In each UIP-like lesion, centrilobular fibrosis could be seen as well as subpleural fibrosis.

The most prevalent histopathological type of lung cancer was squamous cell carcinoma (53%) and all tumors (15 lesions) were located in the peripheral region of the lung (table 3). One patient (case 9) was tentatively diagnosed as unknown primary adenocarcinoma by cervical lymph node biopsy, and finally as lung cancer by postmortem examination. Surgery was performed in 6 out of the 11 patients for the diagnostic or therapeutic purpose of lung cancer. Mutation status regarding EGFR and K-Ras was not examined and EGFR tyrosine kinase inhibitor was not administered. The median survival from the diagnosis of the first lung cancer was 44 ± 42 months. The cause of death was cancer related in 9 patients and CHP related in 2 patients. The primary site of lung cancer was the right lung in 9 (60%) lesions and the left lung in 6. In the right lung, 3 (33%) tumors were located in the upper lobe, 1 (11%) in the middle lobe and 5 (56%) in the lower lobe. In the left lung, 4 (67%) tumors were located in the upper lobe and 2 (33%) in the lower lobe. Regarding the background pathological condition, the tumors were located adjacent to the honeycombing in 7 (47%) of 15 lesions, bullae in 4 (27%) lesions, and relatively normal lung in 4 lesions.

Discussion

We identified 15 lung cancers in 11 patients among 104 patients with CHP, suggesting that the prevalence of lung cancer in CHP seemed to be similar to that in IPF. Since all 11 patients had a smoking history, smoking might have increased the risk of lung cancer in our series. In patients with IPF, most lung cancers develop in the peripheral areas of the lung, where fibrosis is predominant [15]. All 15 lung cancers in CHP developed in the peripheral areas of the lung and more than 70% of cancers were located adjacent to honeycombing and bullae as seen in IPF. In the follow-up of patients with CHP, early detection of lung cancer adjacent to honeycombing and bullae seems to be difficult without chest CT. Most patients in this series tended to have undergone a chest CT once or twice a year.

p53 and p21 genes are overexpressed in hyperplastic bronchial and alveolar epithelial cells not only in IPF but also in CHP [16]. These genes are postulated to play an important role in the inhibition of cellular proliferation and promoting the repair of tissue injury. Chronic DNA damage that leads to p53 gene mutation may be one reason for the high prevalence of lung cancer in CHP as well as IPF because there are several reports concerning alteration of Ras and p53 proteins in IPF patients with lung cancer [17, 18].

The existence of the causative antigens in the peripheral lung in CHP might participate in the development of lung cancer. The size of an antigen is usually less than 3 μm and aerodynamically reaches and deposits in the small airway and alveoli. In BRHP, the causative antigens are derived from pigeon droppings, feathers, sera, egg yolk and egg white, crop fluid and gut wall. Although the detailed mechanism involved in the development of lung cancer is unknown, contact with pet birds was reported to be a potential risk for lung cancer in several epidemiological case-control studies in Europe and the USA [19].

Four patients out of the 11 had a second primary lung cancer. In a review of Japanese cases of lung cancer associated with IPF, there existed 23 cases of synchronous multiple lung cancer. In that series, most tumors were observed in male patients, smokers, and in the peripheral regions of the lung [20]. Similar results were observed in the current study of CHP. In another review of lung cancer with IPF, long-term prognosis in the surgical group was poor because of the high incidence of second primary lung cancer as well as the poor natural history of IPF [21]. In our series in cases 7 and 10, who had died of respiratory failure related to CHP, avoidance of the causative antigen was incomplete because of a delay in the correct diagnosis of CHP. In these 2 cases, the clinical stage of lung cancer was early (IA) and surgical resection was successful. In the management of lung cancer associated with CHP even in the early stage, it is crucial for clinicians to be cautious about the possibility of a second primary lung cancer and persuade the patients to continue to avoid the antigen to prevent the progression of pulmonary fibrosis.

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