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Original Article

Histopathological Type of Lung Cancer and Underlying Driver Mutations in Patients with Chronic Obstructive Pulmonary Disease (COPD) versus Patients with Asthma and COPD Overlap: A Single-Center Retrospective Study

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Abstract

OBJECTIVES: Chronic obstructive pulmonary disease (COPD) increases the risk of lung cancer. The relationships between COPD and Asthma COPD Overlap (ACO), and between the histopathological types of lung cancer and driver mutations remain unclear and need further study. The aim of this retrospective study was to examine the relationships between the histopathological type, frequency of epidermal growth factor receptor (EGFR) driver mutations, and anaplastic lymphoma receptor tyrosine kinase (ALK) rearrangements in the lung cancers of patients with COPD and ACO.

MATERIALS AND METHODS: Patients with pure COPD (n=198) or ACO (n=318) who were admitted to our hospital were reviewed retrospectively.

RESULTS: Lung cancers were identified in 43 (21.7%) patients with pure COPD and 54 (17.0%) patients with ACO. The following lung cancers types were observed: patients with pure COPD had 19 (44.2%) adenocarcinomas, 13 (30.2%) squamous cell lung carcinomas (SCC), 8 (18.6%) small cell lung carcinomas (SCLC); patients with ACO had 23 (42.6%) adenocarcinomas, 23 (42.6%) SCC, 2 (3.70%) SCLC. SCLC was significantly more prevalent in patients with pure COPD ($p<0.05$) than in those with ACO. Differences between the numbers of other histological types of lung cancer and the numbers of driver mutations in the 2 groups of patients were not significant.

CONCLUSION: The differences in the rate of lung cancer and prevalence of EGFR driver mutations between the patients with pure COPD and those with ACO were not significant.

KEYWORDS: Asthma, Chronic obstructive pulmonary disease, Asthma chronic obstructive pulmonary disease overlap, histopathological type, driver mutations

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INTRODUCTION

In Japan, COPD and smoking are the risk factors for the development of lung cancer, especially the squamous cell lung carcinomas (SCC) histological subtype [1, 2]. Asthma increases the risk of SCC and small cell lung carcinoma (SCLC) [3]. Asthma has an inverse association with lung cancer [4]. Atopic diseases are associated with a reduced risk of cancer [5]. Eosinophils appear to have beneficial effects on colorectal carcinoma, oral squamous carcinoma, pulmonary adenocarcinoma, and prostate carcinoma. For example, high eosinophils levels in blood correlate with better outcomes, and nonmetastatic carcinomas are correlated with high levels of eosinophilic infiltration in tumors [6].

Compared to patients with pure COPD or asthma, those with Asthma COPD Overlap (ACO) are known to experience accelerated decline in lung function [7], and increases the risk of hospitalization and disease exacerbations in both asthma and COPD [8]. Few studies have investigated patients with ACO and concomitant lung cancer. The aim of this retrospective study was to examine the relationships between the histopathological types, frequency of epidermal growth factor receptor (EGFR) driver mutations, and anaplastic lymphoma receptor tyrosine kinase (ALK) rearrangements in the lung cancers of patients with COPD and ACO.

MATERIALS AND METHODS

Patients were diagnosed with COPD if they fulfilled the inclusion criteria. In contrast, those who satisfied the exclusion criteria were excluded.

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Inclusion Criteria

1. Outpatients, ≥40 years of age, with a smoking history of >10 pack-year
2. The study period was April 1, 2011, to July 16, 2015. Patients who underwent bronchodilator reversibility test at our hospital were reviewed retrospectively.
3. FEV_1% (forced expiratory volume in one second)<70% post-bronchodilator.

Exclusion Criteria

Patients with any of the following condition were excluded from the study: sinobronchial syndrome, interstitial lung disease, bronchiectasis, tuberculosis, pneumoconiosis, radiation pneumonitis, and bronchiolitis obliterans.

Patients were diagnosed with ACO if they fulfilled the selection criteria stated below, which refers to the "guideline of diagnosis and treatment of COPD 4th edition" published by The Japanese Respiratory Society [9]. Briefly, asthma coexisting with COPD was diagnosed in patients with any of the following conditions: reversible airflow obstruction, elevated fractional exhaled nitric oxide (FeNO) level, elevated immunoglobulin E (IgE) level, and clinical findings.

Selection Criteria

1. FEV_1 after administration of a short-acting bronchodilator ≥12% and ≥200 mL.
2. FeNO ≥37 ppb [10]; FeNO was measured by a portable analyzer (NIOX MINO; Aerocrine, Solna, Sweden) or by a stationary analyzer (CHEST Inc., Tokyo, Japan). The FeNO values determined by the portable analyzer were converted as follows [11]: FeNO (NIOX MINO)=(FeNO (CHEST) - 3.065)/1.278.
3. IgE ≥100 IU/L [12].
4. Clinically diagnosed bronchial asthma (paroxysmal apnea, wheezing, and recurrent coughs).

Ethical Consideration

The study was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study was approved by the Standards of Official Conduct Committee of our hospital (clinical trial number, 2016-008). The requirement for informed consent was waived because the data were examined retrospectively from medical records.

MAIN POINTS

- The relationships between COPD and ACO remain unclear.
- The aim of this retrospective study was to examine the relationships between the histopathological type, frequency of EGFR driver mutations, and ALK rearrangements in the lung cancers of patients with COPD and ACO.
- SCLC more commonly occurred in patients with pure COPD ($p<0.05$). Differences between the numbers of other histopathological types of lung cancer and numbers of driver mutations in the 2 groups of patients were not significant.

Statistical Analyses

Data of age, smoking history, IgE, FeNO, FEV_1%, and %FEV_1 were expressed as mean±standard deviation (SD). The Wilcoxon test was used to compare age, smoking history, IgE, FeNO, FEV_1%, and %FEV between COPD and ACO patients. The chi-square test was used to evaluate the histopathological type of lung cancer and driver mutations.

RESULTS

Figure 1 shows the Consolidated Standards of Reporting Trials diagram of the study. Among all the patients with COPD, 61.6% had ACO (Table 1). The differences between age and sex ratio of the patients with pure COPD and ACO were not significant. The number of pack-years of smoking was higher in patients with pure COPD than in those with ACO (54.6±29.0 pack-years vs. 49.9±31.9 pack-years, respectively; $p<0.05$). IgE level was higher in patients with ACO than in those with pure COPD (470.9±912.4 IU/L vs. 29.9±20.2 IU/L, respectively; $p<0.01$). The FeNO value was higher in ACO patients than in pure COPD patients (39.7±27.4 ppb vs. 18.0±8.6 ppb, respectively; $p<0.01$). FEV_1% was higher in pure COPD patients than in ACO patients (60.9±8.5 vs. 57.2±10.8, respectively; $p<0.01$). %FEV_1 was higher in pure COPD patients than in ACO patients (93.9%±40.3% vs. 78.8%±42.7%, respectively; $p<0.01$). Details of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification for airflow limitation in COPD are shown in Table 1. The risk of lung cancer among pure COPD and ACO patients was 21.7% (43/198) and 17.0% (54/318), respectively, which was not significant (Table 2). The following types of lung cancers were seen: 19 (44.2%) adenocarcinomas, 13 (30.2%) SCC, 8 (18.6%) SCLC, and 1 (2.3%) not otherwise specified (NOS) in 43 patients with pure COPD; and 23 (42.6%) adenocarcinomas, 23 (42.6%) SCC, 2 (3.70%) SCLC, 1 (3.70%) NOS, 1 (1.9%) large cell neuroendocrine carcinoma, 1 (1.9%) large cell carcinoma, and 1 (1.9%) anaplastic carcinoma in 54 patients with ACO. Both patient groups also had 2 cases with unknown types of lung cancer. SCLC was significantly more prevalent in the patients with pure COPD than in those with ACO ($p<0.05$).

EGFR mutations were identified in 25% [3/12, examined in 12 cases of adenocarcinoma and found positive in 3 cases; 2 with an exon point mutation L858R (L858R) and 1 with exon 19 deletion (19del)] of pure COPD patients and 22.2% (4/18; 1 with L858R and 3 with 19del) of ACO patients (Table 2). ALK rearrangements were identified in 0% (0/6), 0% (0/11) of the patients. Differences between the numbers of other histological types of lung cancer and numbers of driver mutations in the 2 groups of lung adenocarcinoma patients were not significant. The difference between the mortality rates in the 2 groups of patients up to April 1, 2016, was not significant (Table 2).

DISCUSSION

COPD and smoking are risk factors for the development of lung cancer, especially the SCC histological subtype in Japan [1, 2]. Moreover, asthma increases the risk of SCC and SCLC [3]. Few studies have investigated the risk of lung cancer in patients with ACO. A cohort study conducted in People's

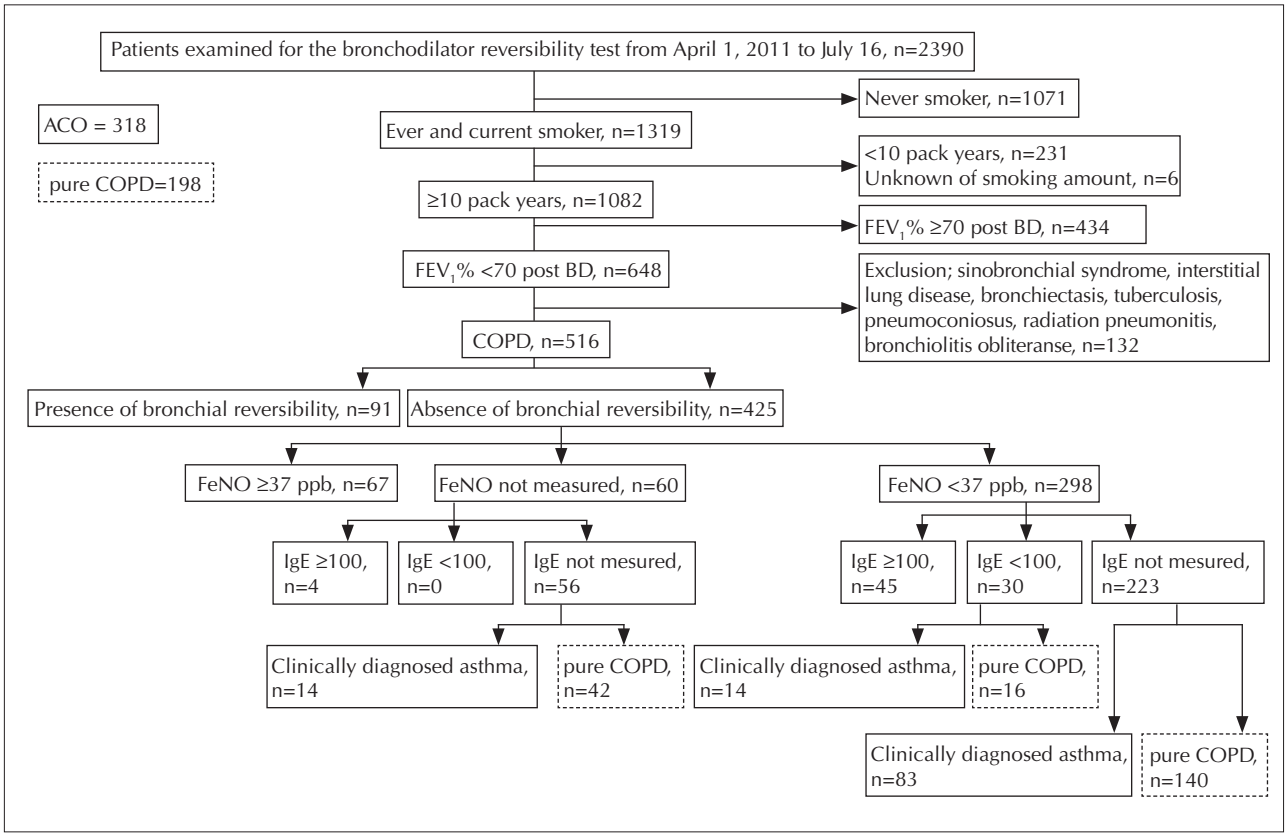

Figure 1. Study design and inclusion and exclusion criteria of ACO and pure COPD
post-BD: post-bronchodilator; line box: ACO; dotted box: pure COPD; ACO: Asthma Chronic obstructive pulmonary disease Overlap; COPD: chronic obstructive pulmonary disease

Table 1. Differential characteristic of patients of pure COPD and ACO

Characteristics	COPD n=516	pure COPD n=198 (38.4%)	ACO n=318 (61.6%)	p
Age, y	69.2±8.3	69.7±8.0	68.9±8.5	N.S
Sex Male	466	184	282	N.S
Female	50	14	36	N.S
Smoking history (pack-years)	51.7±30.9	54.6±29.0	49.9±31.9	p<0.05
IgE (IU/L)	422.3±871.4	29.9±20.2	470.9±912.4	p<0.01
FeNO (ppb)	25.7±23.3	18.0±8.6	39.7±27.4	p<0.01
FEV_1% (%)	58.6±10.1	60.9±8.5	57.2±10.8	p<0.01
%FEV_1 (%)	86.4±42.4	93.9±40.3	78.8±42.7	p<0.01
		I n=126	I n=142	
		II n=54	II n=95	
		III n=8	III n=51	
		IV n=10	IV n=30	

NS: not significant; SD: standard deviation; COPD: chronic obstructive pulmonary disease; ACO: asthma chronic obstructive pulmonary disease overlap; y: years; FeNO: fractional exhaled nitric oxide; FEV1: forced expiratory volume in one second; IgE: immunoglobulin E

Republic of China found that respective men and women with COPD, asthma, and ACO had hazard ratios (HRs) for lung cancer of 1.68 and 1.38, 1.57 and 1.35, and 2.21 and 1.64, respectively; HRs of adenocarcinoma were 1.59 and 1.40, 1.31 and 1.40, 1.76 and 2.36, respectively; HRs of SCC were 1.82 and 1.51, 1.81 and 1.61, 2.21 and 1.64, respectively; HRs of SCLC were 1.57 and 1.61, 1.84 and 1.56, 2.14 and 3.33, respectively [13]. Patients with coexisting pulmonary diseases were more likely to develop any type of lung cancer. However, in this study, the risk of developing SCLC was higher in pure COPD patients. In the same People's Republic of China study, the respective HRs of SCLC for men and women aged 60 to 79 years were 7.16 (95% CI: 6.52-7.86) and 5.71 (95% CI: 4.27-7.63). Age had a greater effect

Table 2. Prevalence of lung cancer and histopathology and genetic assessments in pure COPD and ACO

		pure COPD n=198		ACO n=318	p
Prevalence of malignancy		43 (21.7%)		54 (17.0%)	N.S.
histopathology	SCLC	8 (18.6%)		2 (3.7%)	p<0.05
	Ad	19 (44.2%)		23 (42.6%)	p<0.05
		EGFR	3/12	4/18	N.S.
			L858R; 2	L858R; 1	
			19del1; 1	19del1; 3	
		ALK	0/6	0/11	
	Sq	13 (30.2%)		23 (42.6%)	N.S.
	Others	NOS 1 (2.3%)		NOS 1 (1.9%)	
				LCNEC 1 (1.9%)	
				Large cell carcinoma 1 (1.9%)	N.S.
				Anaplastic carcinoma 1 (1.9%)	
	Unknown	2 (4.7%)		2 (3.7%)	N.S.
Dead		12 (27.9%)		13 (24.1%)	N.S.

Ad: adenocarcinoma; ALK: ALK rearrangement; EGFR: EGFR mutations; LCNEC: large cell neuroendocrine carcinoma; NOS: not otherwise specified; NS: not significant Mean±SD; SCLC: small cell carcinoma; Sq: squamous cell carcinoma

than the coexistence of asthma or COPD. In this study, we selected patients with a history of smoking, but the smoking history of the patients was not reported in the study from the People's Republic of China. The study populations of our study and that of the People's Republic of China are different, and therefore, comparing the results is difficult. In a retrospective Japanese study [14], 23/474 (4.8%) patients with asthma and 15/176 (8.5%) patients with ACO developed lung cancer. The following histopathological types of lung cancer were identified: adenocarcinoma in 78.3%, SCC in 13.0%, and SCLC in 8.7% of asthma patients; SCC in 46.7%, adenocarcinoma in 40.0%, SCLC in 6.7%, and unknown in 6.7% of ACO patients. In Japanese patients with COPD or ACO, a larger study cohort comprising patients with pure asthma is needed to evaluate the risk of lung cancer and histological type. Lim et al. [15] reported that lung cancers in patients with COPD were associated with prevalence of EGFR mutations and ALK rearrangements. The proportions of EGFR mutations and ALK rearrangements decreased as the severity of airflow obstruction increased. Interestingly, in patients with no history of smoking, the prevalence of EGFR mutations was significantly lower in the those with COPD than in those without COPD [15]. In our study, we mainly selected patients with a smoking history longer than a specific duration. We did not examine patients who never smoked.

The Global Initiative for Asthma and GOLD provided the following joint statement. ACO was defined as a syndrome characterized by persistent airflow limitation with several features usually associated with asthma and COPD. A review of the literature on ACO [16] could not find established diagnostic criteria for ACO. For example, reversibility of airflow obstruction and eosinophilia of sputum were used as references [17]. In this study, the prevalence of asthma in patients with COPD was 61.6%. The prevalence was higher than that reported previously. There were three possible explanations for the high prevalence of asthma. First, because of the comparatively older mean age of our study population (69.2±8.3 years). The frequency of ACO increases with age [7, 18]. The prevalence of ACO is higher than 50% in elderly COPD patients. Second, differences between the ACO diagnostic criteria used in our study and those used previously might have resulted an increased prevalence of ACO in our study. With 35 ppb as the cutoff value of FeNO, the prevalence rate of ACO was 16.3% in our COPD population [19]. With both FeNO and IgE ≥ 173 IU/mL, the prevalence rate of ACO was 7.8% [19]. Lastly, during the enrolment of our study patients, we initially evaluated 2390 patients who underwent the bronchodilator reversibility test (Figure 1); moreover, the increased prevalence of ACO in our study cohort might be attributable to selection bias of patients.

This study has several limitations. The first limitation was that we did not examine patients who never smoked. The second limitation was the potential selection bias because we selected patients who had been identified with reversible airflow obstruction.

In conclusion, the difference between patients with pure COPD and those with ACO for the risk of lung cancer was not significant. SCLC more commonly occurred in patients with pure COPD (p<0.05). Differences between the numbers of other histopathological types of lung cancer and numbers of driver mutations in the 2 groups of patients were not significant. This was a small retrospective study, and therefore, an additional prospective study containing patients with pure bronchial asthma is needed to assess the risk of lung cancer and histopathological type. The concept of ACO should be further evaluated and diagnostic criteria for ACO should be established.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kanazawa University Hospital (clinical trial number, 2016-008).

Informed Consent: The requirement for informed consent was waived because the data were examined retrospectively from medical records.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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