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Characteristics of Lung Cancer in Patients with Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease: A Comparative Analysis

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Abstract

Background: The link between IPF (Idiopathic Pulmonary Fibrosis) and Lung Cancer (LC) has been known for years. However, little is known about LC in patients with other Interstitial Lung Diseases (ILD). The aim of this study was to investigate and compare the characteristics and mortality of lung cancer patients with IPF and non-IPF Interstitial Lung Disease (ILD).

Methods: We conducted a retrospective analysis of lung cancer patients with IPF and non-IPF ILD who were managed at our center between 2008 and 2018. Patients with LC diagnosed by a pathology examination were identified. The patient characteristics as well as mortality were recorded.

Results: Twenty-one patients with lung cancer [14 Non-IPF ILD, 7 IPF] were evaluated. Among the patient population, 90.4% were male; the mean age was 67 (range 60-75) years. The most common primary site of lung cancer in both groups was the lower lobe (71.4%, 50% respectively) and the area of fibrosis (85.7%, 78.6%, respectively). The most common histological type was adenocarcinoma (n=10) which was followed by squamous cell carcinoma (n=6). The most common stages were stage III and stage IV (85.7%, 78.6%, respectively) in both groups. During the follow-up period, 8 [2 (28.6%) IPF and 6 (42.9%) non-IPF ILD] patients died in both groups.

Conclusions: The majority of patients was male in both groups. The primary site of cancer was often a fibrotic area and lower lobes of the lungs. The most common histological types were NSCLC including adenocarcinoma and squamous cell carcinoma. The majority of patients had advanced disease at the time of diagnosis. No difference was seen concerning lung cancer characteristics and mortality rate.

Keywords: Idiopathic pulmonary fibrosis; Interstitial lung disease; Lung cancer

Background

Idiopathic Pulmonary Fibrosis (IPF) is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause. It occurs primarily in older adults, is limited to the lungs, and is defined by the histopathological and/or radiological pattern of Usual Interstitial Pneumonia (UIP) [1]. Interstitial Lung Disease (ILD), particularly Idiopathic Pulmonary Fibrosis (IPF), is associated with an increased risk of developing lung cancer (LC). The incidence of LC among patients with IPF is estimated to range from 4.4% to 48% [2-5]. However, little is known about LC in patients with other Interstitial Lung Diseases (ILD). In this context, the purpose of our study was to describe and compare the characteristics of lung cancer patients with IPF and non-IPF ILD using our institutional data registries.

Methods

Patients

We examined the patients diagnosed with interstitial lung disease and lung cancer between January 2008 and December 2018 at our center. All patients underwent High-Resolution CT (HRCT), and 21 patients were also evaluated by thorax CT at

our hospital. CT examinations were performed using a 16 slice-MDCT scanner (Somatom Emotion, Siemens Medical Solutions, Erlangen, Germany). The HRCT images were obtained using the following parameters: 270 mAs and 120 kVp, slice thickness, 1 mm; contiguous 0.75-mm collimation. High Resolution Computed Tomography (HRCT) and thorax CT images of all ILD patients were evaluated and recorded by an experienced radiologist. At our center the diagnosis of ILD is based on the clinical criteria recommended by the American Thoracic Society and the European Respiratory Society [1,6]. Patients diagnosed with ILD were divided into two groups as IPF and non-IPF ILD. Non-IPF ILD refers to ILD caused by a disease other than IPF. Baseline demographics of all the patients including, age, gender, smoking history, follow-up duration, types of Non-IPF ILD, steroid treatment, and mortality were recorded.

Lung cancer was classified according to the World Health Organization classification [7]; LC staging was based on the 7th edition of the TNM classification of malignant tumors [8]. Histopathological findings, staging, location of primary lesions, and metastasis were recorded for all patients with LC.

Statistical analysis

Statistical analyses of the study data were performed using SPSS 17.0 software package. Categorical variables were reported as number and percentage; continuous measurements were reported as mean ± standard deviation or median (minimum-maximum). Chi-square test or Fisher's exact test was used to compare categorical variables. Comparison of continuous variables between the study groups was performed by the independent samples t-test for the variables meeting the criteria of parametric distribution, and by Mann Whitney U test for the variables with non-parametric distribution. Statistical significance was set at $p < 0.05$.

Results

Patient characteristics

We identified 21 patients with lung cancer [7 IPF, 14 non-IPF ILD] from the medical records between 2008 and 2018. Three patients were excluded from the study because they had a lung nodule or mass on chest CT scan without a pathological diagnosis. Baseline demographic characteristics of the patients are shown in Table 1. Nineteen (90.4%) patients were male and 2 (9.5%) were female; their mean age was 67 years. Smoking rate was substantially high in both groups (85.7%). The underlying cause in the non-IPF ILD-LC group was determined in 2 patients (rheumatoid arthritis, systemic sclerosis). The majority of patients did not receive steroid treatment. During the follow-up period, 8 [2 (28.6%) IPF and 6 (42.9%) non-IPF ILD] patients died. There was no statistically significant difference between the two groups in terms of demographic characteristics.

The characteristics of lung cancer in patients with IPF and non-IPF ILD are shown in Table 2. In both groups, the location of the lung cancer was predominantly lower lobe (71.4%, 50%, respectively) and a fibrotic area (85.7%, 78.6%, respectively). The most common histological type was adenocarcinoma (n=10) followed by squamous cell carcinoma (n=6) and small cell LC (n=3). Cancer stage distribution was also similar in both groups; the most common stages were stage III and stage IV (85.7%, 78.6%, respectively). The most common organ metastasis was to bone (28.5%) in the non-IPF lung cancer group. There was no statistically significant difference between the two groups in terms of demographic characteristics and mortality.

	IPF with LC		**Non-IPF ILD with LC**		**p-value**
	N	Results	N	Results	
Age at diagnosis (years),median	7	65 (60-75)	14	67 (60.75-71.25)	0.824
Gender M/W (male %)	7	7/0(100)	14	12/2(85.7)	0.293
Observation periods, months	7	30(12-48)	14	45(38-60)	0.109
Smoking	7		14		0.725
Never		1 (14.2%)		2 (14.2%)	
Former		4 (57.2%)		10 (71.4%)	
Current		2 (28.6%)		2 (14.2%)	
Non IPF ILD type not specified	7	0	14	12 (85.7%)	
Rheumatoid arthritis		0		1 (7.1%)	
Systemic sclerosis		0		1 (7.1%)	
Steroids	7	1 (14.2%)	14	5 (35.7%)	0.306
Without steroids		6 (85.8%)		9 (64.3%)	0.306
Mortality over observation period (%)	7	2 (28.6%)	14	6 (42.9%)	0.525
N: Patient number; İPF: Idiopathic Pulmonary Fibrosis; ILD: Interstitial Lung Diseases; LC: Lung Cancer					

Table 1: Baseline demographics of patients with IPF-LC and Non-IPF ILD –LC.

Variable	IPF with LC		Non-IPF ILD with LC		p-value
	N	Results	N	Results	
Laterality	7		14		0.361
Left	7	5 (71.4%)	14	6 (42.9%)	
Right	7	2 (28.6%)	14	8 (57.1%)	
Bilateral	7	-	14	-	
Fibrotic area	7	6 (85.7%)	14	11 (78.6%)	
Primary site	7		14		0.540
Upper lobe-peripheral		2 (28.6%)		6 (42.9%)	
Lower lobe-peripheral		5 (71.4%)		7 (50%)	
Others		-		1 (7.1%)	
Histology	7		14		0.535
SCC		2 (28.6%)		4 (28.6%)	
Adenocarcinoma		4 (57.1%)		6 (42.9%)	
Small cell ca		-		3 (21.4%)	
Others		1 (14.2%)		5 (35.7%)	
Stage	7		14		0.287
I		1 (14.2%)		-	
II		-		3 (21.4%)	
III		4 (57.1%)		6 (42.9%)	
IV		2 (28.6%)		5 (35.7%)	
Metastasis	7		14		0.103
Brain		1 (14.2%)		-	
Malignant pleural effusion		1 (14.2%)		1 (7.1%)	
Bone		-		4 (28.5%)	
N: Patient number, SCC: Squamous cell					

Table 2: Comparison of the characteristics of lung cancer in patients with IPF and non-IPF ILD.

The lung cancer computed tomography findings of the two patients with interstitial pulmonary fibrosis are shown in Figures 1 and 2.

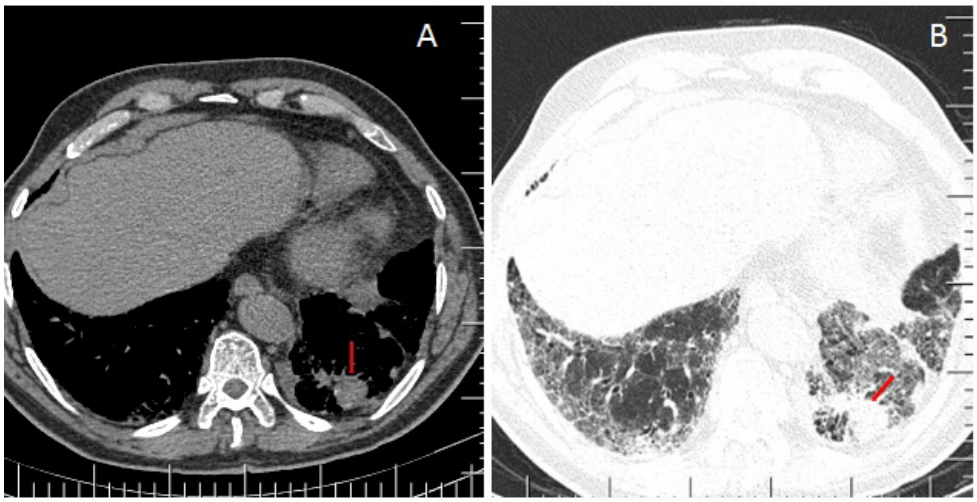

Figure 1: A 64-year-old man with interstitial pulmonary fibrosis and pathologically confirmed diagnosis of lung adeno cancer. A-B: Axial high resolution CT image obtained at the level of the lung base shows ground glass opacity and reticular densities. Axial high resolution CT and mediastinal window image show a mass with soft tissue density at the periphery of the left lower lobe (open arrow).

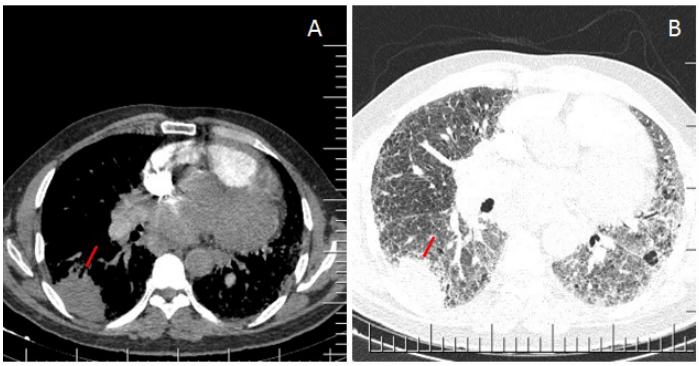

Figure 2: A 72-year-old man with non-interstitial pulmonary fibrosis interstitial lung disease and pathologically confirmed diagnosis of small cell lung cancer A-B: Axial high resolution CT image obtained at the level of the lung base shows ground glass opacity and reticular densities. Axial high resolution CT and mediastinal window image show a mass with soft tissue density at the periphery of the right lower lobe (open arrow).

Discussion

The aim of this study was to identify and compare the characteristics of lung cancer patients with IPF and non-IPF Interstitial Lung Disease (ILD). Interstitial Lung Disease (ILD), particularly Idiopathic Pulmonary Fibrosis (IPF), is associated with an increased risk of developing lung cancer (LC) [2-4]. On its own, pulmonary fibrosis is a risk factor for lung carcinogenesis [9-11]. Moreover, elder age, male sex, history of smoking, and coexisting emphysema are also strong risk factors that contribute to developing LC in IPF patients [12-14]. In our study, the majority of patients with non-IPF ILD were male. The smoking history was common in both groups and the tumor frequently appeared in the fibrotic area.

In the general population, the predominant type of lung cancer is Non-Small Cell Lung (NSCLC) cancer. It is also the most common type of lung cancer in patients with IPF. In addition, adenocarcinoma is the most common subtype of histological NSCLC in the general population [15,16]. Most of the recent studies have shown that squamous cell carcinoma is the most common type of lung cancer, whereas adenocarcinoma is the second most common type in IPF patients, especially in the peripheral lower lobes [17-19]. In our study, the predominant lung cancer type was NSCLC in patients with IPF. However, adenocarcinoma was the most common type while squamous cell carcinoma was the second most common type. We think that this resulted from a small number of patients.

Cancer risk in the non-IPF ILD population is well known. Some phenotypes of non-IPF ILD including rheumatoid arthritis [20], polymyositis/dermatomyositis [21], and systemic sclerosis [22] are known to be associated with increased risk for lung cancer. Although the pathogenic mechanisms underlying LC development in non-IPF ILD remain unknown, chronic inflammation and a fibrotic environment are thought to contribute to tumorigenesis [23,24]. In addition, several studies have shown that chronic inflammation can initiate tumor development by causing DNA damage or by sensitizing cells to mutations [25]. However, little is known about LC in patients with other Interstitial Lung Disease (ILD). In our study, the majority of patients with non-IPF-ILD had no identified disease subtype and the ICD code of mixed connective tissue disease was recorded for such patients. There are also common areas of bilateral fibrosis in the lungs in this group.

Watanebe, et al. reported that lung cancer occurring in patients with connective tissue disease was more common in peripheral and lower lobes; they also showed that the most common histological type was adenocarcinoma and that the cancer was diagnosed at an advanced stage [26]. Similarly, in our study, lung cancer was frequently located in peripheral fibrotic areas and lower lobes in patients with non-IPF-ILD, with the most common histological type being adenocarcinoma that was diagnosed at an advanced stage.

Recent studies have argued that the mortality of lung cancer in patients with IPF is higher than for lung cancer alone, and that the presence of IPF is associated with a prognosis worse than lung cancer per se [18,27]. Similarly, various studies have shown that lung cancer development reduces survival in patients with connective tissue disease-related interstitial lung disease [22,26]. In our study, the mortality rates in patients with IPF and non-IPF-ILD were 28.6% and 42.9%, respectively. Mortality was associated with cancer in both groups.

In general, our data suggest that lung cancer in IPF and non-IPF ILD is phenotypically distinct from “Sporadic” lung cancer.

This study had some limitations. First, it was a retrospective, single-center study. Secondly, the number of patients was small. Therefore, we believe that future multicenter studies are warranted.

Conclusions

The majority of patients with lung cancer with IPF and non-IPF-ILD were male, older, and smokers. The primary site of cancer was often in the fibrotic area and lower lobes. The most common histological types were NSCLC types including adenocarcinoma and squamous cell carcinoma. The majority of patients had advanced cancer at the time of diagnosis. There was no difference in demographics, lung cancer characteristics, and mortality in both groups.

Author’s contribution: In the article, Professor Şule Akçay has contributed to literature support, findings and structuring of tables and figures, and additional contributions in writing discussion.

Professor Zafer Koç contributed to the formation of figures that evaluated the radiological findings of all cases.

Conflict of interest: None to declare.

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