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Lung cancer development in patients with connective tissue disease–related interstitial lung disease

A retrospective observational study

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Abstract

Previous studies have reported that patients with idiopathic pulmonary fibrosis occasionally develop lung cancer (LC). However, in connective tissue disease (CTD)-related interstitial lung disease (ILD), there are few data regarding the LC development. The aim of the present study was to evaluate the clinical significance of LC development in patients with CTD-ILD. A retrospective review of our database of 562 patients with ILD between 2000 and 2014 identified 127 patients diagnosed with CTD-ILD. The overall and cumulative incidences of LC were calculated. In addition, the risk factors and prognostic impact of LC development were evaluated. The median age at the ILD diagnosis was 63 years (range 37–84 years), and 73 patients (57.5%) were female. The median follow-up period from the ILD diagnosis was 67.4 months (range 10.4–322.1 months). During the period, 7 out of the 127 patients developed LC (overall incidence 5.5%). The cumulative incidences at 1, 3, and 5 years were 0.0%, 1.8%, and 2.9%, respectively. The risk of LC development was significantly higher in patients with higher smoking pack-year (odds ratio [OR] 1.028; 95% confidence interval [CI] 1.008–1.049; $P = 0.007$) and emphysema on chest high-resolution computed tomography (OR 14.667; 95% CI 2.871–74.926; $P = 0.001$). The median overall survival time after developing LC was 7.0 months (95% CI 4.9–9.1 months), and the most common cause of death was LC, not ILD. According to the Cox proportional hazard model analysis with time-dependent covariates, patients who developed LC showed significantly poorer prognosis than those who did not (hazard ratio 87.86; 95% CI 19.56–394.67; $P < 0.001$). In CTD-ILD, clinicians should be careful with the risk of LC development in patients with a heavy smoking history and subsequent emphysema. Although not so frequent, the complication could be a poor prognostic determinant.

Abbreviations: CI = confidence interval, CTD = connective tissue disease, CTD-ILD = connective tissue disease–related interstitial lung disease, DM = dermatomyositis, FVC = forced vital capacity, HRCT = high-resolution computed tomography, ILD = interstitial lung disease, IPF = idiopathic pulmonary fibrosis, LC = lung cancer, OR = odds ratio, PM = polymyositis, RA = rheumatoid arthritis, SjS = Sjögren syndrome, SLE = systemic lupus erythematosus, SSc = systemic sclerosis, UIP = usual interstitial pneumonia.

Keywords: connective tissue disease, interstitial lung diseases, lung cancer

1. Introduction

Idiopathic pulmonary fibrosis (IPF), pathologically usual interstitial pneumonia (UIP), is the majority of idiopathic interstitial lung diseases (ILDs).[1] Patients with IPF occasionally develop lung cancer (LC) with the overall incidence of 2.7% to 43.1%,[2–8] which is highly variable because of the differences in observation periods and inclusion criteria by retrospective approaches. Smoking history, higher smoking pack-year, aging, male gender, and presence of emphysema have been suggested as the risk factors for developing LC.[2,3,5,9,10] In addition, a recent study demonstrated that the LC development had a poor prognostic impact on patients with IPF.[3]

Connective tissue disease (CTD) comprises a group of chronic and systemic autoimmune disorders, such as rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis or dermatomyositis (PM/DM), Sjögren syndrome (SjS), and systemic lupus erythematosus (SLE). CTDs frequently involve lungs, among which ILD is a common manifestation. Recent large-scale studies

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reported that CTD patients had a high risk of LC development compared with general population.[11–15] In addition, several researchers have suspected that the presence of ILD would have an association with LC development in CTD patients,[16–18] although conflicting data have also been reported.[19,20] These previous studies, on the contrary, included all CTD patients with and without ILD. Therefore, the data focused on LC development in CTD-related ILD (CTD-ILD) are scarce. To our knowledge, only 2 studies of CTD-ILD cohorts reported the overall incidence of LC as 8.8% and 12.3%,[21,22] but the clinically important concerns, such as the risk factors and prognostic influence, have not been studied. The aim of the present study was to evaluate the clinical significance of LC development in patients with CTD-ILD.

2. Methods

2.1. Study subjects

This study was approved by the Institutional Review Board of the Hamamatsu University School of Medicine (approval number 15-197). Because of the retrospective nature of the study, written consent from participants for the use of records was waived.

A retrospective review of our database of 562 consecutive patients with ILD between 2000 and 2014 at the Hamamatsu University Hospital in Japan identified 151 patients who were diagnosed with CTD-ILD. Among them, 21 patients were excluded because their follow-up period was less than 6 months. In addition, 3 patients were excluded due to the insufficient data. Finally, 127 patients with CTD-ILD were included in the present study. The diagnosis of ILD was based on the existence of bilateral reticulation, ground-glass attenuation, or consolidation on high-resolution computed tomography (HRCT), in which cases with apparent pulmonary infection or other pulmonary diseases were excluded. At the time of this study, the diagnoses of CTDs were reconfirmed using the criteria of each CTD.[23–28] All the patients underwent regular follow-up with radiological examinations of chest X-ray and/or HRCT at least every 6 months.

2.2. Data collection

Clinical data at the time of ILD diagnosis, such as demographic data, smoking history, laboratory data, pulmonary function test results, and bronchoalveolar lavage fluid results, were retrospectively obtained from the medical record review. In addition, the development of LC (including histology according to the World Health Organization and clinical stage by the TNM system) and the clinical course were also recorded.

Two pulmonologists (KY and KN) who had no knowledge of the patients' clinical information evaluated the following findings on the chest HRCT images taken at the time of CTD-ILD diagnosis: the presence of emphysema; the compatibility for UIP pattern. In the present study, the presence of emphysema was defined as a low-attenuation hypovascular area generally without visible walls, occupying ≥10% of the total lung area.[29] The UIP pattern was defined as subpleural and basal-predominant reticulation with radiological honeycombing and without atypical findings for IPF, such as extensive ground-glass attenuation and profuse micronodules.[1] In addition, in patients who developed LC, the location of the primary mass was evaluated as follows: peripheral or central; fibrotic, emphysematous, or normal area of the lung. The peripheral location was defined as <3 cm from the pleura. Disagreements between the 2 reviewers were resolved by consensus.

2.3. Statistical analysis

Data were described as a number (percentage) or median (range). The overall incidence of LC was defined as the total occurrence rate of LC until June 30, 2015. The cumulative incidence of LC was evaluated at 1, 3, and 5 years of follow-up using the Gray test, with a consideration of death not associated with LC as a competing factor.[30] Logistic analyses were performed to identify the risk factors for developing LC. The overall survival time was defined as the time from the date of a diagnosis of CTD-ILD to the date of all-cause death or censoring. Patients were censored if alive on June 30, 2015 or at the time of being a dropout. The prognostic impact of developing LC was evaluated by using Cox proportional hazard model analysis with time-dependent covariates. A value of $P < 0.05$ was considered to be significant. Statistical analyses were performed using R software version 2.15.1 (The R Foundation for Statistical Computing, Vienna, Austria) and SPSS software version 13.0 (SPSS, Chicago, IL).

3. Results

3.1. Baseline characteristics at CTD-ILD diagnosis

Baseline characteristics at the time of CTD-ILD diagnosis are summarized in Table 1. The median age was 63 years (range 37–84 years), and 73 patients (57.5%) were female. About half a

Table 1

Baseline characteristics at the diagnosis of CTD-ILD.

	Total (n = 127)	LC (−) (n = 120)	LC (+) (n = 7)
Age, y	63 (37–84)	62.5 (37–84)	66 (47–72)
Male	54 (42.5%)	49 (40.8%)	5 (71.4%)
Current or former smoker	72 (52.0%)	66 (55.0%)	6 (85.7%)
Smoking dose (pack-year)	5 (0–144) (n = 125)	0 (0–144)	50 (0–100)
PaO_2 on room air, Torr	78 (37–103) (n = 110)	77 (37–103)	81 (66–85)
KL-6, U/mL	792.5 (220–7339) (n = 112)	772 (220–7339)	1023 (566–1310)
% predicted FVC, %	77.1 (33.6–122.3) (n = 116)	76.9 (33.6–122.3)	81.1 (61.5–106.0)
% predicted DLco, %	72.1 (26.6–148.2) (n = 50)	71.9 (26.6–148.2)	75.9 (75.9–75.9)
BALF-lymphocyte, %	6.2 (0.2–73.0) (n = 93)	6.2 (0.2–73.0)	4.8 (4.5–8.0)
Emphysema on HRCT	14 (11.0%)	10 (8.3%)	4 (57.1%)
UIP pattern on HRCT	27 (21.3%)	25 (20.8%)	2 (28.6%)

Data are presented as n (%) or median (observed range). BALF = bronchoalveolar lavage fluid, DLco = diffusing capacity of the lung for carbon monoxide, FVC = forced vital capacity, HRCT = high-resolution computed tomography, KL-6 = Krebs von den Lungen-6, LC = lung cancer, UIP = usual interstitial pneumonia.

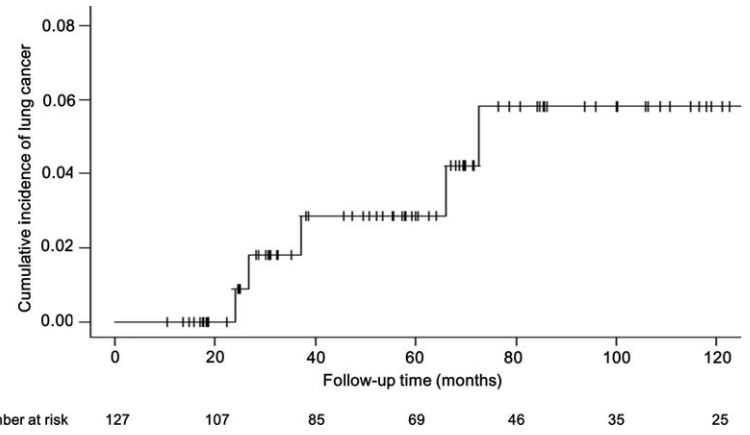

Figure 1. Cumulative incidence for lung cancer in patients with connective tissue disease–related interstitial lung disease.

number of patients had a smoking history. Most patients showed mildly deteriorated PaO_2, forced vital capacity (FVC), and diffusing capacity for carbon monoxide. The breakdown of CTDs was as follows: RA alone (n = 39), PM/DM alone (n = 37), SSc alone (n = 17), SjS alone (n = 17), PM/DM + SjS (n = 3), SSc + SjS (n = 3), RA + SSc + SjS (n = 2), RA + SjS (n = 2), PM/DM + SSc + SjS + SLE (n = 2), RA + SSc (n = 1), PM/DM + SSc + SLE (n = 1), PM/DM + SSc (n = 1), PM/DM + SLE (n = 1), and SjS + SLE (n = 1). The majority of patients had either component of RA or PM/DM.

3.2. Development of LC

The median follow-up period from the time of CTD-ILD diagnosis was 67.4 months (range 10.4–322.1 months). During the follow-up period, 7 patients developed LC (overall incidence 5.5%). All the diagnoses of LC were made after the diagnosis of CTD-ILD. The cumulative incidences of LC at 1, 3, and 5 years were calculated as 0.0%, 1.8%, and 2.9%, respectively (Fig. 1). As shown in Table 1, patients who developed LC had higher smoking pack-year and frequently showed emphysema on HRCT. Table 2 summarizes the overall incidence of LC in each CTD component. LC development was the most frequent in patients with SSc component (3/27; 11.1%), followed by those with RA component (2/44; 4.5%) and those with PM/DM component (2/45; 4.4%).

In logistic analyses (Table 3), the higher smoking pack-year and the presence of emphysema were significantly associated with LC development in patients with CTD-ILD (odds ratio [OR] of smoking pack-year 1.028; 95% confidence interval [CI] 1.008–1.049; $P = 0.007$, OR of emphysema 14.667; 95% CI 2.871–74.926; $P = 0.001$). Differences in CTD components, treatment status for ILD, severity of ILD including FVC and PaO_2, and UIP compatibility on HRCT showed no statistically significant associations with LC development.

3.3. Clinical course and prognosis

The backgrounds of LC development and the clinical course are summarized in Table 4. The 7 CTD-ILD patients developed LC at least 2 years after ILD diagnosis (median 66.1 months, range 24.1–206.3 months). All but 1 had heavy smoking histories with more than 40 pack-year. The most frequent LC histology was small-cell carcinoma (4/7: 57.1%), which was observed in patients with RA (n = 2) and PM/DM (n = 2). The primary lesions of LC were commonly located on the peripheral area with fibrotic or emphysematous changes on HRCT. Among the 7 patients who developed LC, 4 received interventions for LC treatment including surgery and/or systemic chemotherapy. In contrast, the remaining 3 patients received only palliative care mainly due to the poor performance status. The median overall survival time after developing LC was 7.0 months (95% CI 4.9–9.1 months), and the most common cause of death was LC, not ILD (according to the descriptions in death certificates). Patients who developed LC showed significantly poorer prognosis than those who did not (hazard ratio 87.86; 95% CI 19.56–394.67; $P < 0.001$).

4. Discussion

We evaluated the overall and cumulative incidences of LC in patients with CTD-ILD and identified the risk factors as higher smoking pack-year and presence of emphysema on HRCT, using a relatively large cohort with a long-term follow-up period. In addition, our results suggest that LC development could be a poor prognostic determinant in CTD-ILD.

In our cohort of CTD-ILD, the overall incidence of LC was 5.5%, and the cumulative incidences were calculated as 0.0%, 1.8%, and 2.9% at 1, 3, and 5 years, respectively. The values were unexpectedly low and even comparable to the recently reported lifetime risk of LC or bronchus cancer development in general population (approximately 6.6% according to 2010–2012 data from National Cancer Institute).[31] In patients with IPF, on the other hand, the overall incidence of LC was reported as 2.7% to 43.1%,[2–8] and the cumulative incidences were as 3.3% at 1 year and 15.4% at 5 years from our institution[2]; 41% at 1 year and 82% at 3 years by Tomassetti et al,[3] which seems apparently higher than our results of

Table 2

Overall incidence of LC according to each component of CTD.

Disease component	Lung cancer/total
Rheumatoid arthritis	2/44 (4.5%)
Polymyositis or dermatomyositis	2/45 (4.4%)
Sjögren syndrome	0/30 (0.0%)
Systemic sclerosis	3/27 (11.1%)
Systemic lupus erythematosus	0/5 (0.0%)

Values are the number of patients (%). Cases of overlapping components are counted repeatedly.

Table 3

Univariate logistic analyses of risk factors for developing LC in patients with CTD-ILD.

Factor	OR	95% CI	*P*
Age, per 1-y increase	1.002	0.930–1.081	0.953
Male	3.622	0.675–19.431	0.133
Current or former smoker	6.000	0.701–51.357	0.102
Smoking dose, per 1-pack-year increase	1.028	1.008–1.049	0.007
PaO_2 on room air, per 1-Torr increase	0.990	0.919–1.067	0.789
KL-6, per 1-U/mL increase	1.000	0.999–1.001	0.892
% Predicted FVC, per 1% increase	1.012	0.967–1.059	0.599
BALF-lymphocyte, per 1% increase	0.929	0.738–1.169	0.530
Emphysema on HRCT	14.667	2.871–74.926	0.001
UIP pattern on HRCT	1.520	0.278–8.304	0.629
RA component	0.743	0.138–3.995	0.729
PM/DM component	0.716	0.133–3.850	0.697
SSc component	3.000	0.629–14.310	0.168
Corticosteroids administration	0.728	0.133–3.953	0.711
Immunosuppressants administration	0.132	0.015–1.129	0.064

BALF = bronchoalveolar lavage fluid, CI = confidence interval, FVC = forced vital capacity, HRCT = high-resolution computed tomography, KL-6 = Krebs von den Lungen-6, OR = odds ratio, PM/DM = polymyositis or dermatomyositis, RA = rheumatoid arthritis, SSc = systemic sclerosis, UIP = usual interstitial pneumonia.

CTD-ILD. The comparison between those previous data and ours suggests that LC development in CTD-ILD is not so frequent and the screening, in comparison with that for IPF, can be focused on patients who would have a high risk for the development.

Smoking history, higher smoking pack-year, aging, male gender, and presence of emphysema are known as risk factors for LC development in patients with IPF.[2,3,5,9,10] However, in the case of CTD-ILD, the risk factors have not been studied. Although the statistical limitation due to the small number of patients who developed LC should be taken into consideration, the present study is the first to demonstrate that higher smoking pack-year and emphysema can be the candidates even in CTD-ILD. Smoking would have a common influence on the risk of LC development, regardless of the background ILDs. Regarding the pathogenesis of LC development, there has been a speculation that the effect of immunosuppressants for CTD treatment may cause LC.[32] However, in our data, administration of immunosuppressants did not show a statistically significant association with LC development. In CTD, the pathogenesis of LC development other than smoking effects remains unclear.

In our results, interestingly, LC development was observed only in patients with components of SSc, RA, and PM/DM. Our results are comparable to the data of literature review by Yang et al[17] reporting that LC development in the published cases of

Table 4

Summary of background and clinical course in patients with CTD-ILD who developed LC.

Patient number	1	2	3	4	5	6	7
CTD	SSc	SSc	SSc	RA	RA	DM	DM
Gender	Female	Male	Male	Male	Female	Male	Male
Smoking dose, pack-year	0	70	100	48	40	50	69
Emphysema on HRCT	No	Yes	Yes	Yes	No	Yes	No
Age at LC diagnosis, y	64	64	78	73	73	58	69
Duration from ILD diagnosis to LC diagnosis, mo	206.3	114.8	66.1	24.1	72.5	26.6	37.2
Immunosuppressive treatment for ILD at LC diagnosis	Corticosteroid	None	None	Corticosteroid	Corticosteroid	Corticosteroid	Corticosteroid; cyclosporin
Oxygen supplement at LC diagnosis	No	No	Yes	No	Yes	Yes	No
Histology of LC	AD	AD	SQ	SM	SM	SM	SM
Clinical stage of LC	IV	I	IV	I	IV	IV	IV
Location of primary lesion	Undetermined*	Left; lower lobe; peripheral; on fibrosis	Left; upper lobe; peripheral; on emphysema	Right; middle lobe; peripheral; on emphysema	Right; upper lobe; peripheral; on emphysema	Right; lower lobe; peripheral; on fibrosis	Left; upper lobe; peripheral; on emphysema
Intervention for LC	Palliative care	Surgery	Palliative care	Surgery	Palliative care	Chemotherapy	Surgery and subsequent chemotherapy
Outcome	Dead	Alive	Dead	Dead	Dead	Dead	Dead
Cause of death	LC	–	LC	Gastrointestinal bleeding after LC surgery	LC	LC	Rupture of aortic aneurysm

AD = adenocarcinoma, CTD = connective tissue disease, DM = dermatomyositis, ILD = interstitial lung disease, LC = lung cancer, RA = rheumatoid arthritis, SM = small-cell carcinoma, SQ = squamous cell carcinoma, SSc = systemic sclerosis.

* Due to bilateral and multiple consolidations by invasive mucinous adenocarcinoma.

CTDs (with and without ILD) was the most frequent in those with SSc. Also in a recent study, the similar result has been reproduced.[18] Presence of specific CTD components, particularly SSc, may increase the risk of LC development, although our cohort and study design could not prove the hypothesis (Table 3). Significantly, our patients who developed LC would be largely affected by their heavy smoking histories. In addition, the majority of LC histology in our patients was small-cell carcinoma, which is inconsistent with the data of those previous studies.[17,18] On the contrary, these imply a bias of our cohort. Further researches are necessary to compare the risk of LC development among CTDs, in which several confounding factors, such as gender, age, smoking history, treatment status, and presence/absence of emphysema and ILD, should be adjusted.

CTD-ILD patients who developed LC showed poorer prognosis than those who did not. One of the explanations for the poor prognosis would be that 5 of the 7 patients who developed LC in our cohort were diagnosed at clinical stage of IV. As aforementioned, the majority of LC histology was small-cell carcinoma, suggesting the difficulty in early detection due to the rapid growth of tumors. In addition, the primary lesions of LC were commonly located on peripheral areas of the lungs. These patients would be less symptomatic in spite of their advanced stage of LC. These factors might lead to the diagnosis delays. Furthermore, 3 of the 7 patients did not receive any intervention for LC. The untreated patients, all with clinical stage of IV, commonly exhibited a poor performance status because of the old age, respiratory failure by the ILD, and/or other comorbidities, as well as LC itself. In general, patients with preexisting ILD are known to have a risk for the chemotherapy-associated acute exacerbation of ILD, which can be a lethal complication as we have recently reported.[33,34] Our clinicians and the patients would give more weight to the risk. The management of LC in each situation might affect the prognosis, although it is debatable whether ILD patients with incurable LC can receive the true benefit from systemic chemotherapy.

A major limitation of the present study is the possible presence of biases and inevitable confounding factors in the small, retrospective, and single-institution data. Larger, prospective, and multicenter studies are warranted to confirm our preliminary findings.

In conclusion, in patients with CTD-ILD, a heavy smoking history and emphysema on HRCT may be the risk factors for developing LC. Although not so frequent, the event could be a poor prognostic determinant; early detection and appropriate management are needed.

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