Serum KL-6 Levels in Lung Cancer Patients With or Without Interstitial Lung Disease

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Background: It is not known whether lung cancer patients with interstitial lung disease (ILD) might have higher serum levels of KL-6, a high molecular weight glycoprotein classified as a polymorphic epithelial mucin. In addition, prognosis of these patients with elevated serum KL-6 levels might be poorer than that with normal KL-6 levels, but it has not been well clarified. **Methods:** Serum KL-6 levels in 273 lung cancer patients with or without ILD, and prognostic significance of elevated serum KL-6 levels in these patients were studied using uni- and multivariate analyses. **Results:** Serum KL-6 levels were elevated (>500 U/ml) in 73.5% of lung cancer patients with ILD and

in 33.7% of those without ILD. Serum KL-6 levels in lung cancer patients with ILD were significantly higher than those without ILD. In lung cancer patients with ILD, elevated serum KL-6 has no prognostic significance, but in those without ILD, however, it was one of the unfavorable prognostic factors. **Conclusions:** Elevated serum KL-6 levels can be observed in lung cancer patients both with and without ILD. Having ILD has strong prognostic impact in patients with lung cancer. In those without ILD, however, elevated KL-6 levels may be related to poor prognosis. *J. Clin. Lab. Anal.* 24:295–299, 2010. © 2010 Wiley-Liss, Inc.

Key words: lung cancer; interstitial lung disease; KL-6

INTRODUCTION

Cigarette smoking and occupational exposures are common contributors not only to lung cancer but also to interstitial lung disease (ILD), such as idiopathic pulmonary fibrosis (IPF) (1,2). KL-6 is a high molecular weight glycoprotein classified as a polymorphic epithelial mucin (MUC1) (3). Although an essential epitope structure recognized by anti-KL-6 MAb remains unclear, glycosylation at Thr/Ser residues of the tandem-repeating MUC1 peptides seems to determine the disease-associated antigenic structures of KL-6 (3). Elevated serum KL-6 levels were observed in patients with ILD, irrespective of the etiology of ILD (4–10). Therefore, measurement of serum KL-6 is now widely accepted as a diagnostic test to monitor the activity of ILDs (4–10). However, KL-6 was originally introduced as a tumor marker for lung cancer (11) and not known whether lung cancer patients with ILD might have higher serum levels of KL-6. In addition, prognosis of these patients with elevated serum KL-6 levels might be

poorer than that with normal KL-6 levels, but it has not been well clarified. In this study, we evaluated serum KL-6 levels in lung cancer patients with or without ILD and prognostic significance of elevated serum levels of KL-6 in them.

PATIENTS AND METHODS

Subjects

Nine hundred and forty-five patients with newly diagnosed primary lung cancer who were admitted to the Division of Respiratory Medicine, Tsukuba Medical Center Hospital, from 1999 to 2009, were retrospectively analyzed. In this study, 273 of 945 consecutive lung

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cancer patients who received serum assay for KL-6 were included. The diagnosis of lung cancer was confirmed in each patient using pathologic specimens. Pathologic diagnosis was defined by the WHO classification (12) and patients were classified using the TNM staging system (13). ILD was diagnosed on the basis of medical history, physical examination, and abnormalities compatible with bilateral lung fibrosis detected on conventional CT or HRCT, such as peripheral reticular opacities in both lungs (14,15).

Measurement of KL-6 Levels

Serum KL-6 levels were measured by a sandwich type enzyme-linked immunosorbent assay technique using a KL-6 antibody kit (Eisai, Tokyo, Japan). The recommended cut-off value was determined at 500 U/ml from the levels of healthy individuals reported earlier (11).

Statistical Methods

The Mann–Whitney *U* test was applied to elucidate the difference between the two independent groups, and proportion was compared by the chi-square test. The Kaplan–Meier method was used to assess survival curves and the log-rank test to evaluate the statistical significance of differences found between the two groups. The multivariate Cox proportional hazard model was also used in this study. $P < 0.05$ was considered significant.

RESULTS

Characteristics of Patients

The characteristics of 273 lung cancer patients are shown in Table 1. Their ages ranged from 21 to 93 years (median: 70 years). Two hundred thirty-six (87.5%) were ex- or current smokers. The lung cancers were composed of 144 adenocarcinomas, 83 squamous cell carcinomas, 5 large cell carcinomas, and 41 small cell carcinomas. Seventy-eight patients had stage IA–IIB, 98 patients had stage IIIA–B, and 97 patients had stage IV disease.

Of the 273 patients, 68 (24.9%) patients were evaluated as having ILD. Table 2 shows histology, clinical stage, and therapy for lung cancer patients with or without ILD. There was no statistical significant difference in them between these two groups of patients. Prognosis of 68 lung cancer patients with ILD was, however, poorer than that of 205 lung cancer patients without ILD (Fig. 1; Table 3)

Comparison in KL-6 Levels Between Lung Cancer Patients With or Without ILD

Serum KL-6 levels were elevated (> 500 U/ml) in 50 (73.5%) of 68 lung cancer patients with ILD, but only in

TABLE 1. Characteristics of 273 Patients With Lung Cancer

Age (years)	Median: 70, range: 21–93
Gender	
Male	231 (84.6%)
Female	42 (15.4%)
Interstitial pneumonia	
Present	68 (24.9%)
Absent	205 (75.1%)
Histology	
Adenocarcinoma	144 (52.8%)
Squamous cell carcinoma	83 (30.4%)
Large cell carcinoma	5 (1.8%)
Small cell carcinoma	41 (15.0%)
Clinical stage	
IA–IIB	78 (28.6%)
IIIA–B	98 (35.9%)
IV	97 (35.5%)
Treatment	
Surgery	75 (27.5%)
Chemotherapy	80 (29.3%)
Chemo-radiotherapy	38 (13.9%)
Irradiation	25 (9.2%)
Supportive care	55 (20.1%)

TABLE 2. Differences Between Lung Cancer Patients With ILD and Those Without ILD

	Patients with ILD	Patients without ILD	<i>P</i> -value
Number of patients	68	205	
Histology			
AD	35	109	0.8887
Non-AD	33	96	
Clinical stage			
IA–IIIB	46	130	0.5616
IV	22	75	
Treatment			
Surgery	14	61	0.1603
Other	54	144	

ILD, interstitial lung disease; AD, adenocarcinoma.

Fig. 1. Survival of lung cancer patients with ILD (bold line) and without ILD. There was statistical significant difference between them ($P = 0.001$, Logrank test).

TABLE 3. Multivariate Analyses of Prognostic Factors in Lung Cancer Patients Without ILD

Factor	Multivariate analysis		
	(Cox's proportional hazard model)		
	Hazard ratio	95% CI	P-value
Age (70 $\geq$ vs. >70 years)	0.80	0.35–1.82	0.599
Gender (female vs. male)	0.94	0.62–1.41	0.778
Performance status (0–2 vs. 3–4)	0.99	0.42–2.35	0.994
Smoking habit (absent vs. present)	0.20	0.11–0.38	0.001
Pathology (non-SCLC vs. SCLC)	0.96	0.55–1.67	0.890
Stage (IA-IIA vs. IIB-IV)	0.09	0.04–0.19	0.001
KL-6 (normal vs. elevated level)	0.58	0.38–0.90	0.001

95% CI, 95% confidence interval; SCLC, small cell lung cancer; ILD, interstitial lung disease.

69 (33.7%) of 205 lung cancer patients without ILD. Serum KL-6 levels in 68 lung cancer patients with ILD were significantly higher than those without ILD ($P = 0.0001$, Mann–Whitney U test, Fig. 2). In 40 lung cancer patients without ILD who had elevated serum KL-6 levels more than 1,000 U/ml, 35 (87.5%) patients had lung adenocarcinoma and 36 (90%) were those with metastatic disease.

Survival and KL-6 Levels in Lung Cancer Patient With or Without ILD

In 68 lung cancer patients with ILD, prognosis of those with elevated serum KL-6 levels was not poorer than that with normal KL-6 levels (Fig. 3).

In 205 lung cancer patients without ILD, however, there was statistical significant difference in survival between those with elevated serum KL-6 and those with normal levels of KL-6 (Fig. 4). In both uni- and multivariate analyses of the noninvasive variables, elevated serum KL-6 (>500 U/ml) was one of the unfavorable prognostic factors.

DISCUSSION

Lung cancer is still one of the most common fatal malignancies (16). Despite the progress made in various therapeutic modalities, the overall outcome of lung cancer patients remains poor and has not decreased to a level where we can be satisfied (17). Similarly, no standard therapy for ILDs has established yet, although they themselves are not a malignant disease. In this study, we evaluated the clinical significance of the serum KL-6 levels in lung cancer patients with or without ILD and found three notable findings. First, the positive rate as well as serum KL-6 level in lung cancer patients with ILD was significantly higher than those without ILD. The origin and mechanism of elevated serum levels of KL-6 is not known clearly, but it is evaluated that serum

Fig. 2. Serum KL-6 levels in 68 lung cancer patients with ILD and those in 205 lung cancer patients without ILD.

KL-6 may mainly be derived from lung cancer cells as well as type II pneumocytes (18). In patients with both diseases, lung cancer cells and type II pneumocytes might be related to the elevation of serum KL-6 levels, although the ratio and mechanism were not known. Second, uni- and multivariate analyses clearly showed its prognostic significance in lung cancer patients without ILD in this study. In lung cancer patients without ILD who had elevated serum KL-6 levels more than 1,000 U/ml, 87.5% patients had adenocarcinoma and 90% had metastatic disease. As a background, KL-6

Fig. 3. Survival of lung cancer patients with ILD who had elevated serum KL-6 levels (bold line) and normal KL-6 levels.

Fig. 4. Survival of lung cancer patients without ILD who had elevated serum KL-6 levels (bold line) and normal KL-6 levels. There was statistical significant difference between them ($P = 0.001$, Logrank test).

was originally introduced as a tumor marker for lung cancer (11), and patients with lung adenocarcinoma and those with metastatic disease had higher serum KL-6 levels than those with non-adenocarcinoma and those with early stage diseases (11). KL-6 is now used as a serum marker for ILDs with various etiologies because elevated serum KL-6 levels has reported many kinds of ILDs, such as IPF, collagen disease-associated pulmonary fibrosis, and radiation pneumonitis (19,20). Some previous authors evaluated prognostic significance of its elevated serum levels (11,21). Kohno et al. reported that pretreatment evaluation of serum KL-6 level could predict survival in patients with IPF (11). We had earlier evaluated serum KL-6 levels in patients with ILDs and revealed that elevated KL-6 level might provide valuable information by which to identify ILD patients with increased risk for subsequent mortality (21). These results suggested that KL-6 is a prognostic factor in

patients with ILDs. On the other hand, however, prognostic significance of KL-6 in patients with lung cancer has scarcely been reported (22), although its prognostic significance in lung cancer patients with radiation pneumonitis was only reported (19,20). Third, in lung cancer patients with ILD, our results showed that elevated serum KL-6 levels were not one of the unfavorable prognostic factors. This was an unexpected result and we could not clearly explain the reason. We only speculated that elevated serum levels of KL-6 in lung cancer patients with ILD might be associated with complex mechanisms and origins of its elevation in these two diseases.

In this study, we found the above-mentioned three novel findings, but there were some limitations. The study was retrospective, spanning a long study period, and included only 273 of 745 consecutive lung cancer patients. We cannot exclude the possibility of variations owing to sampling or bias in the patient selection. Therefore, a large cohort study will be required to confirm our results.

In summary, elevated serum KL-6 levels can be observed in lung cancer patients both with and without ILD. In lung cancer patients without ILD, elevated serum levels may be related to poor prognosis. It is necessary for physicians to pay attention to these patients in the evaluation of serum KL-6 levels.

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