Increased lung cancer risk in patients with interstitial lung disease and elevated CEA and CA125 serum tumour markers

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ABSTRACT

Background and objective: The aetiology and pathogenesis of interstitial lung disease (ILD) and ILD combined with lung cancer (ILD-CA) are unclear. We aim to investigate serum tumour marker (STM) levels and to explore their predictive and diagnostic value of cancer in ILD.

Methods: Fifty-eight patients with ILD-CA, 632 with ILD only and 628 with acute respiratory illness were studied. Serum levels of carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), CA125 and neuron-specific enolase (NSE) were measured.

Results: All STM levels were elevated in ILD-CA compared with ILD group (P < 0.01). CEA and CA125 levels were significantly higher in ILD than in controls (P < 0.01). After adjustment for gender, age and smoking, ILD-CA risk in the CEA and CA125 fourth quartiles was increased compared with the first quartiles (CEA: odds ratio (OR) = 8.7, 95% confidence interval (CI) = 2.0–37.6; CA125: OR = 9.8, 95% CI = 2.3–42.7). Receiver operating characteristic (ROC) curve analysis in patients with ILD-CA showed a cut-off points of 3.99 ng/mL for CEA and 35.00 U/mL for CA125 with sensitivities of 74.6% and 71.9%, specificities 70.4% and 66.1%, and the areas under the curve 0.76 (95% CI = 0.69–0.82) and 0.75 (95% CI = 0.69–0.81), respectively.

Conclusions: Serum CEA and CA125 levels are often elevated in ILD patients. The risk of cancer in ILD is increased with an elevation of serum CEA and CA125 levels. Serum CEA and CA125 levels may be a marker of cancer in ILD patients.

SUMMARY AT A GLANCE

Serum tumour markers are often elevated in patients with interstitial lung disease (ILD). We investigate patients with both ILD and cancer. CEA and CA125 discriminate patients with only ILD from patients with ILD and cancer with good sensitivity, specificity and accuracy. CEA and CA125 may be markers to detect cancer in patients with ILD.

Key words: carbohydrate antigen 19-9, carcinoembryonic antigen, idiopathic pulmonary fibrosis, interstitial lung disease, lung cancer.

Abbreviations: BALF, bronchoalveolar lavage fluid; CA, lung cancer; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; CVD, collagen vascular disease; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSCLC, non-small-cell lung cancer; OR, odds ratio; ROC, receiver operating characteristic; SCC, squamous cell carcinoma.

INTRODUCTION

Interstitial lung disease (ILD) comprises a heterogeneous group of disorders characterized by acute or chronic lung inflammation and fibrosis involving the interstitium. About two-thirds of ILD cases are idiopathic, while the remainders are associated with a variety of aetiologies (including pollutants, drugs, connective tissue disease, infection and malignancy). The most common types of ILD are idiopathic interstitial pneumonias (IIP) in particular idiopathic pulmonary fibrosis (IPF).1 Lung cancer (CA) risk is increased in patients with ILD, and the two diseases often occur concomitantly.2 Studies have shown a high incidence of CA in patients with ILD (9.8–38% vs 2–6.4% in controls).3 CA incidence is increased 4.96-fold in patients with IPF compared with the general
population after adjustment for age, gender and smoking habit. IIP is also associated with increased CA risk. Collagen vascular disease-associated ILD (CVD-ILD) may be a predisposing factor for pulmonary malignancy.

The aetiology and pathogenesis of ILD and IIP with CA (ILD-CA) remain unclear. IPF may be considered a neoproliferative lung disorder. In fact, IPF has fundamental pathogenic hallmarks of CA such as genetic alterations, uncontrolled mesenchymal cell proliferation and tissue invasion behaviour, and dysregulated intracellular signalling pathways. The concept of IPF being a premalignant lung disorder may be used to explore links between these two diseases.

Tumour markers are commonly elevated in patients with CA and can be used for case finding and disease monitoring. Various tumour markers are elevated in patients with ILD, including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), squamous cell carcinoma (SCC) antigen, cytokeratin 19 fragment and Krebs von den Lungen-6.

The objectives of the present study are to investigate serum tumour marker levels in different types of ILD and in ILD-CA, to define the relationship between serum tumour marker levels and the risks of cancer in ILD, and to explore the diagnostic value of serum tumour markers for ILD-CA.

METHODS

Study population

The study protocol was approved by the Human Ethics Review Committee of the Beijing Chao-Yang Hospital, China. Written informed consent was obtained from all patients. Male and female patients with ILD were selected from the database of the Beijing Institute of Respiratory Medicine Interstitial Lung Disease Group, Beijing Chao-Yang Hospital, affiliated to the Capital Medical University. In our hospital, all patients suspected of having ILD undergo a standard investigation protocol, and detection of serum tumour markers is performed in all patients with ILD. ILD was defined according to the British Thoracic Society IIP guidelines and the American Thoracic Society and European Respiratory Society Consensus Classification of IIP: (i) compatible clinical manifestations; (ii) lung function and gas exchange impairment; (iii) chest high-resolution computed tomography (HRCT) abnormalities; (iv) laboratory findings; and (v) bronchoalveolar lavage fluid (BALF) profiles and/or transbronchial lung biopsy or surgical lung biopsy pathological features.

A total of 1307 consecutive patients were diagnosed with ILD between January 2003 and December 2009. Patients were excluded if: (i) chest HRCT, lung function, blood gas analysis or serum tumour marker data were missing; (ii) ILD was due to known pulmonary aetiology (e.g. pollutants, drugs or radiation); or (iii) another benign disease possibly affecting the results (e.g. cirrhosis, cholecystitis or gastrointestinal bleeding) or cancer (other than pulmonary) were also present (Fig. 1). Of the patients initially screened, 632 were included in this cross-sectional study. These patients were further classified into IPF (n = 214), non-IPF IIP (n = 97), CVD-ILD (n = 163) and other types/unclassified ILD (n = 158) groups. The 97 non-IPF IIP cases included 61 cryptogenic organized pneumonia, 22 non-specific interstitial pneumonia, 5 respiratory bronchiolitis ILD, 2 acute interstitial pneumonia, 1 lymphocytic interstitial pneumonia and 6 unclassified disease. The 163 cases of CVD-ILD included 44 rheumatoid arthritis, 43 Sjögren’s syndrome, 21 polymyositis and dermatomyositis, 55 of systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease, vasculitis and unclassified connective tissue disease. The 158 cases of other ILD included 110 unclassified, 18 sarcoidosis, 13 pulmonary alveolar proteinosis, 9 pulmonary lymphangioleiomymatosis and 8 pulmonary histiocytosis X. A total of 58 cases had ILD-CA, including 25 adenocarcinoma, 15 SCC, 9 small cell carcinoma or 9 other cancer types (Fig. 1).

A total of 628 patients hospitalized during the same period for other respiratory diseases, including
Tumour markers in interstitial lung disease

Table 1  Demographic data of patients and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>ILD</th>
<th>IPF</th>
<th>Non-IF P IIP</th>
<th>CVD-ILD</th>
<th>Other ILD</th>
<th>ILD-CA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n)</td>
<td>632</td>
<td>214</td>
<td>97</td>
<td>163</td>
<td>158</td>
<td>58</td>
<td>628</td>
</tr>
<tr>
<td>Male (%)</td>
<td>54.0</td>
<td>75.7</td>
<td>49.5</td>
<td>30.1</td>
<td>51.9</td>
<td>82.8*</td>
<td>54.0</td>
</tr>
<tr>
<td>Age (year)</td>
<td>61.3 ± 12.6</td>
<td>63.7 ± 9.7</td>
<td>58.0 ± 13.7</td>
<td>61.0 ± 11.7</td>
<td>60.5 ± 11.5</td>
<td>70.1 ± 7.9*</td>
<td>61.3 ± 12.7</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>148 (23.4)</td>
<td>62 (29.0)</td>
<td>20 (20.6)</td>
<td>24 (14.7)</td>
<td>42 (26.6)</td>
<td>30 (51.7)*</td>
<td>172 (27.4)</td>
</tr>
<tr>
<td>Ex</td>
<td>155 (24.5)</td>
<td>76 (35.5)</td>
<td>16 (16.5)</td>
<td>33 (20.3)</td>
<td>30 (19.0)</td>
<td>21 (36.2)*</td>
<td>157 (25.0)</td>
</tr>
<tr>
<td>Never</td>
<td>329 (52.1)</td>
<td>76 (35.5)</td>
<td>61 (62.9)</td>
<td>106 (65.0)</td>
<td>86 (54.4)</td>
<td>7 (12.1)*</td>
<td>303 (48.2)</td>
</tr>
<tr>
<td>Smoking index (pack-years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>329 (52.1%)</td>
<td>76 (35.5%)</td>
<td>61 (62.9%)</td>
<td>106 (65.0%)</td>
<td>86 (54.4%)</td>
<td>7 (12.1%)*</td>
<td>303 (48.2%)</td>
</tr>
<tr>
<td>1–399</td>
<td>106 (16.8%)</td>
<td>47 (22.0%)</td>
<td>14 (14.4%)</td>
<td>19 (11.7%)</td>
<td>26 (16.5%)</td>
<td>6 (10.3%)*</td>
<td>98 (15.6%)</td>
</tr>
<tr>
<td>400–799</td>
<td>98 (15.5%)</td>
<td>46 (21.5%)</td>
<td>12 (12.4%)</td>
<td>14 (8.6%)</td>
<td>26 (16.5%)</td>
<td>14 (24.1%)*</td>
<td>102 (16.2%)</td>
</tr>
<tr>
<td>800–1199</td>
<td>72 (11.4%)</td>
<td>27 (12.6%)</td>
<td>6 (6.2%)</td>
<td>22 (13.5%)</td>
<td>17 (10.8%)</td>
<td>22 (37.9%)*</td>
<td>79 (12.6%)</td>
</tr>
<tr>
<td>1200+</td>
<td>27 (4.3%)</td>
<td>18 (8.4%)</td>
<td>4 (4.1%)</td>
<td>2 (1.2%)</td>
<td>3 (1.9%)</td>
<td>9 (15.5%)*</td>
<td>50 (7.9%)</td>
</tr>
</tbody>
</table>

* P < 0.01 compared with ILD and control groups.

CVD-ILD, collagen vascular disease associated to interstitial lung disease; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; ILD-CA, interstitial lung disease associated to lung carcinoma; IPF, idiopathic pulmonary fibrosis.

chronic obstructive pulmonary disease (n = 287), pneumonia (n = 161), bronchiectasis (n = 99) and bronchial asthma (n = 81), were selected as controls. The controls were matched with the ILD cases for age, gender and smoking status, and had no history or indications of ILD or cancer.

Tumour markers

Tumour markers were analysed for all included patients. Serum was obtained from a fasting blood sample. CEA, CA19-9, CA125 and neuron-specific enolase (NSE) were measured by an electrochemiluminescence immunoassay, using a Roche Hitachi Cobas e601 (Hitachi, Tokyo, Japan). The normal ranges used were CEA < 3.40 ng/mL, CA19-9 < 35.00 U/mL, CA125 < 35.00 U/mL and NSE < 17.5 ng/mL.

Statistical analysis

Data were analysed using SPSS 16.0 (SPSS, Inc., Chicago, IL, USA). Categorical data were analysed using χ² tests. Normally distributed continuous variables are presented as means ± standard deviations. Non-normally distributed variables were presented as medians and interquartile ranges, and were log-transformed before analyses to normalize their distribution. Continuous variables were analysed using analysis of variance, and differences between each pair of groups were determined using Student’s t-tests. Multivariate logistic regression was used to adjust for confounders. Serum tumour markers were divided into quartiles. The diagnostic value of the tumour markers was evaluated with receiver operating characteristic (ROC) curve analyses. A P-value < 0.05 was considered statistically significant.

RESULTS

Demographic data

There were no differences in age, gender, smoking status and smoking index between patients with ILD and controls. Patients with ILD and cancer were older, more often male, and had a proportion of smokers and a higher smoking index than in those with ILD only (P < 0.01) (Table 1).

Serum tumour markers

Serum levels of CEA, CA19-9, CA125 and NSE were elevated in patients with ILD-CA compared with patients with ILD and controls (P < 0.001). CEA and CA125 levels in patients with ILD were higher than in controls (P < 0.01). No differences were observed in CA19-9 and NSE levels between ILD and controls (Table 2).

Serum tumour markers in ILD subgroups

CEA levels were highest in patients with IPF (P < 0.01), higher in other ILD than in non-IPF IIP (P < 0.01) and control (P < 0.05) groups, but not significantly different between non-IPF IIP, CVD-ILD and control (Table 3) groups. Similarly, CA19-9 levels were highest in patients with IPF (P < 0.01), without significant differences between the other groups. CA125 levels were higher in the IPF group than in the non-IPF IIP and control (P < 0.01) groups, but not different from the IPE; other ILD or CVD-ILD groups; CA125 levels in the other ILD group were higher than in controls (P < 0.05), with no differences between non-IPF IIP; CVD-ILD and control groups. NSE levels were comparable across groups.

Serum tumour markers as ILD-CA predictors

The relationship between tumour markers and risk of ILD-CA was assessed in 58 ILD-CA cases and 632 ILD by dividing tumour marker levels into quartiles. The proportion of patients with ILD-CA increased with increasing CEA, CA125 and CA19-9 levels separated by quartiles (P < 0.01 for CEA and CA125, P < 0.05 for CA19-9) (Table 4). No significant associations were observed for NSE levels.
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Logistic regression analyses showed that compared with patients with ILD in the 1st CA19-9 quartile, the relative ILD-CA risk in the 2nd, 3rd and 4th quartile increased 1.5-, 6.0- and 16.1-fold, respectively. After adjustment for gender, age and smoking, ILD-CA risk was significant for the 4th quartile only (odds ratio (OR) = 8.65, 95% confidence interval (CI) = 1.99–37.56). Similarly, compared with patients with ILD in the 1st CA19-9 quartile, the relative ILD-CA risk for patients in the 4th quartile was increased twofold. After adjustment for gender, age and smoking, CA19-9 levels were no longer associated with ILD-CA (OR = 1.56, 95% CI = 0.69–3.49). Compared with patients with ILD in the 1st CA125 quartile, the relative ILD-CA risk in the 4th quartile was increased 15-fold. After adjustment for gender, age and smoking, ILD-CA risk in patients in the 4th quartile was increased (OR = 9.84, 95% CI = 2.27–42.65). NSE levels did not increase ILD-CA risk.

Using the recommended normal CEA level of <3.40 ng/mL as the cut-off, CEA sensitivity was significantly higher in patients with ILD-CA than in those with ILD (77.6% vs 46.5%, P < 0.01). CEA sensitivity and specificity for ILD-CA diagnosis were 77.6% and 53.8%, respectively. The best cut-off point was 3.99 ng/mL: sensitivity was 74.6% and specificity was 70.4%. Diagnostic accuracy was moderate (AUC of 0.758 (95% CI = 0.694–0.822)) (Table 5).

CA19-9 sensitivity was not different between patients with ILD-CA and ILD (32.8% and 23.7%, respectively). Using the recommended normal CA19-9 level of <39.0 U/mL as the cut-off, sensitivity was 32.8%, and specificity was 76.3%. The ILD-CA diagnostic accuracy was low (AUC = 0.596; 95% CI = 0.523–0.669) (Table 5).

CA125 sensitivity was significantly higher in patients with ILD-CA than in patients with ILD (71.9% vs 34.0%, P < 0.01). Using the recommended normal CA125 level of <35.0 U/mL as the cut-off, sensitivity was 71.9%, and specificity was 66.1%. Diagnostic accuracy was moderate (AUC = 0.748; 95% CI = 0.686–0.809) (Table 5).

NSE sensitivity was higher in patients with ILD-CA than in patients with ILD (42.9% vs 26.9%, P < 0.05). Using the recommended normal NSE level of <17.5 ng/mL as the cut-off, sensitivity was 42.9% and specificity was 73.0%. Diagnostic accuracy was low (AUC = 0.621; 95% CI = 0.528–0.715) (Table 5).

### Table 2 Comparison of serum tumour markers among three groups

<table>
<thead>
<tr>
<th>Tumour markers</th>
<th>Controls, n = 628</th>
<th>ILD, n = 632</th>
<th>ILD-CA, n = 58</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA (ng/mL)</td>
<td>2.6 (1.8, 3.8)</td>
<td>3.1 (1.6, 6.2)*</td>
<td>8.0 (3.8, 18.0)*‡</td>
<td>0.001</td>
</tr>
<tr>
<td>CA19-9 (U/mL)</td>
<td>12.7 (8.2, 19.9)</td>
<td>14.9 (6.3, 35.6)</td>
<td>20.1 (9.6, 88.2)*‡</td>
<td>0.001</td>
</tr>
<tr>
<td>CA125 (U/mL)</td>
<td>15.6 (10.0, 30.1)</td>
<td>22.0 (11.5, 48.2)*</td>
<td>55.7 (32.5, 127.9)*‡</td>
<td>0.001</td>
</tr>
<tr>
<td>NSE (ng/mL)</td>
<td>12.4 (10.4, 15.2)</td>
<td>14.2 (11.5, 18.0)</td>
<td>16.3 (12.1, 31.0)*‡</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* P < 0.01 compared with control group; † P < 0.05 compared with the ILD; ‡ P < 0.01 compared with the ILD. P-value was obtained using multiple linear regression after adjustment for gender, age and smoking factors.

ILD, interstitial lung disease; ILD-CA, interstitial lung disease associated to lung carcinoma; CEA, carcinoembryogenic antigen; CA19-9, carbohydrate antigen 19-9; CA125, cancer antigen 125; NSE, neuron-specific enolase.

### Table 3 Comparison of serum tumour markers in ILD subgroups

<table>
<thead>
<tr>
<th>Tumour markers</th>
<th>Control group, n = 628</th>
<th>Non-IPF ILD, n = 97</th>
<th>CVD-ILD, n = 163</th>
<th>Other ILD, n = 158</th>
<th>IPF, n = 214</th>
<th>P₁</th>
<th>P₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA (ng/mL)</td>
<td>2.6 (1.8, 3.8)</td>
<td>1.8 (1.1, 4.1)</td>
<td>2.4 (1.4, 4.3)</td>
<td>3.1 (1.7, 6.1)*‡</td>
<td>4.8 (2.7, 8.5)*</td>
<td>0.001</td>
<td>0.66</td>
</tr>
<tr>
<td>CA19-9 (U/mL)</td>
<td>12.7 (8.2, 19.9)</td>
<td>10.3 (6.6, 18.8)</td>
<td>11.2 (4.3, 28.2)</td>
<td>14.8 (5.9, 27.9)</td>
<td>22.5 (8.9, 83.6)*</td>
<td>0.001</td>
<td>0.18</td>
</tr>
<tr>
<td>CA125 (U/mL)</td>
<td>15.6 (10.0, 30.1)</td>
<td>15.6 (9.2, 26.3)</td>
<td>23.4 (10.9, 48.1)</td>
<td>21.9 (11.6, 53.0)*‡</td>
<td>27.4 (13.5, 57.8)*</td>
<td>0.001</td>
<td>0.08</td>
</tr>
<tr>
<td>NSE (ng/mL)</td>
<td>12.4 (10.4, 15.2)</td>
<td>13.3 (11.0, 16.5)</td>
<td>13.9 (10.5, 19.1)</td>
<td>14.2 (12.3, 19.0)</td>
<td>14.2 (11.5, 17.8)</td>
<td>0.09</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* P < 0.01 compared with the other ILD, CVD-ILD, non-IPF IIP and the control group; † P < 0.01 compared with non-IPF IIP and the control group; ‡ P < 0.05 compared with the control group.

P₁ was obtained using analysis of variance and analysis of covariance; P₂ was obtained using multiple linear regression after adjustment for gender, age and smoking factors.

CEA, carcinoembryogenic antigen; CA19-9, carbohydrate antigen 19-9; CA125, cancer antigen 125; CVD-ILD, collagen vascular disease associated to interstitial lung disease; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; ILD-CA, interstitial lung disease associated to lung carcinoma; IPF, idiopathic pulmonary fibrosis; NSE, neuron-specific enolase.
DISCUSSION

The present study assessed whether tumour markers could serve as diagnostic and prognostic tools. Serum CEA, CA19-9, CA125 and NSE levels were higher in patients with ILD-CA than in patients with ILD.ILD subtype analysis revealed that serum CEA, CA19-9 and CA125 levels were elevated in patients with IPF. Elevated CEA and CA125 were associated with increased ILD-CA risk. This suggests that CEA, CA19-9 and CA125 tumour markers not only increase the likelihood of cancer, they are also increased in fibrosis and may indicate a future cancer risk.

CEA and CA19-9 levels are also significantly increased in BALF from patients with IIP and are related to the BALF neutrophil proportion. It seems that BALF CEA measurements may be useful to estimate the degree of pathological changes and IIP activity. CEA staining is present in the epithelia of respiratory bronchioles and alveoli of patients with IIP, and is especially increased in alveoli where type II pneumocytes proliferate. CA19-9 is a marker of pancreatic cancer, rectal cancer and other tumours, and is commonly used in gastrointestinal cancer diagnosis. A study has reported significantly elevated CA19-9 levels in BALF from 24 patients with ILD (16 IPF and 8 CVD-ILD cases) and a correlation with neutrophil count.

The diagnostic specificity of serum CA125 for cancer is poor, and CA125 will also increase in some inflammatory diseases. The relationship between CA125 and ILD is unclear. Studies have shown a worse prognosis for patients with non-small-cell lung cancer and elevated baseline CA125 levels, and a prognostic value for CA125 in operable early cancer; however, the exact role of CA125 in cancer...
management is still controversial.\textsuperscript{25,26} Nevertheless, our results show raised CA125 levels in patients with ILD and that elevated levels are associated with increased risk of developing cancer.

The efficacy of therapeutic approaches for IPF is low, and the prognosis is usually poor. The pathological features and quasi-malignant course of IPF may be associated with elevated tumour markers. Most studies report that sarcoidosis increases CA risk,\textsuperscript{5,27} but it is unclear if tumour markers are elevated in sarcoidosis. Hirakata \textit{et al}. showed that serum and BALF CEA and CA19-9 levels were elevated in pulmonary alveolar proteinosis and that CA19-9 levels reflected disease severity.\textsuperscript{28} CVD-ILD and non-IPF IIP serum tumour markers did not increase, suggesting that serum tumour marker levels reflect the process and extent of lung fibrosis.

In conclusion, serum CEA and CA125 levels are elevated in patients with ILD, especially IPF, and are further elevated in patients with ILD and cancer. The risk of cancer in patients with ILD is increased with an elevation of serum CEA and CA125 levels. Serum CEA and CA125 have the potential to assist the diagnoses of cancer in ILD. They may have a role in screening patients with ILD for CA or identifying patients with ILD at risk of developing cancer.

\textbf{Acknowledgements}

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