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Associations between serum carcinoembryonic antigen levels and adenocarcinoma subtypes of the lung

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ABSTRACT

Background: Increased serum carcinoembryonic antigen (CEA) levels have been associated with a poor outcome in lung cancer. The aim of this study was to further clarify the associations between CEA levels and adenocarcinoma subtypes.
Patients and methods: We retrospectively assessed preoperative serum CEA levels and clinicopathological factors in 307 consecutive patients who underwent resection for primary lung adenocarcinoma with curative intent.
Results: Subtypes included adenocarcinoma in situ (AIS) in 20 cases, minimally invasive adenocarcinoma (MIA) in 20, invasive mucinous adenocarcinoma (IMA) in three, lepidic predominant adenocarcinoma (LPA) in 41, papillary predominant adenocarcinoma (PPA) in 106, acinar predominant adenocarcinoma (APA) in 90, solid predominant adenocarcinoma (SPA) in 23, and micropapillary predominant adenocarcinoma (MPA) in four. Serum CEA levels varied according to gender, age, smoking status, clinical stage, lymph node metastasis, pathological stage, and adenocarcinoma subtype. Serum CEA levels were higher in the APA, MPA, IMA, and SA subtypes than in the AIS, MIA, PPA, and LPA subtypes. Multiple regression analysis revealed that the clinical stage and adenocarcinoma subtype were significantly associated with serum CEA levels. Univariate analysis demonstrated that preoperative CEA levels were significantly associated with both the postoperative disease-free survival (DFS) and overall survival. Cox regression analysis revealed that the clinical stage and adenocarcinoma subtype were significantly associated with the postoperative DFS.
Conclusion: The serum CEA level was elevated in advanced disease stages and certain adenocarcinoma subtypes, suggesting the usefulness of CEA as a marker reflecting the malignant behavior of lung adenocarcinomas.

1. Introduction

Carcinoembryonic antigen (CEA) was first identified as an oncofetal protein of colon cancer in 1965 [1]. More recent studies have revealed that the human CEA family comprises 35 genes tandemly arranged within the same chromosomal region (19q13.2–13.4) [2]. Importantly, CEA, also known as CEA-related cell adhesion molecule 5, is frequently associated with a poor clinical outcome in malignant tumors through a variety of mechanisms, including the promotion of invasion, dissemination, metastasis, and immune suppression via the interactions between cell surface receptors and the suppression of dendritic cells and natural killer (NK) cells, which function in tumor immunity [3]. In lung cancer, CEA is expressed in both non-small cell lung cancer (NSCLC) and SCLC and is thought to be associated with an adverse prognosis in NSCLC [4]. Most studies have reported higher serum CEA levels in lung adenocarcinoma than in other histological types of NSCLC [5,6], with some conflicting results indicating higher levels in squamous cell carcinoma [7,8], presumably due to the influence of a smoking history.

In 2011, new histopathological classification criteria of lung adenocarcinoma were proposed by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) [9]. In these new criteria, invasive adenocarcinomas are classified according to the predominant pattern. The 2015 classification of lung cancer published by the World Health Organization employs the proposed subtypes of the IASLC/ATS/ERS criteria [10], which include adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA),

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lepidic predominant adenocarcinoma (LPA), acinar predominant adenocarcinoma (APA), papillary predominant adenocarcinoma (PPA), micropapillary predominant adenocarcinoma (MPA), solid predominant adenocarcinoma (SPA), and rare variants of invasive adenocarcinomas, consisting of invasive mucinous adenocarcinoma (IMA), colloid adenocarcinoma (CA), fetal adenocarcinoma (FA), and enteric adenocarcinoma (EA).

Because the relationship between serum CEA levels and lung adenocarcinoma subtypes was unknown, we retrospectively analyzed patients who underwent surgery for primary lung adenocarcinoma to clarify the clinicopathological significance of serum CEA levels, as defined by the proposed subtypes. To the best of our knowledge, this is the first report to clarify the associations between serum CEA levels and the newly defined lung adenocarcinoma subtypes.

2. Patients and methods

2.1. Patients

The study protocol was approved by the Institutional Review Board of our institution. We retrospectively reviewed the medical records of 307consecutive patients who underwent resection for lung adenocarcinoma with curative intent, with available data for preoperative serum CEA levels from April 2008 to December 2013. Patients who received preoperative induction therapy or those with synchronous multiple lung cancers were excluded. Final adenocarcinoma subtyping was obtained from resected lung specimens. Staging was assessed according to the most recent criteria provided by the American Joint Committee on Cancer, the Union for International Cancer Control, and the IASLC [11], using ^{18}F-fluorodeoxyglucose-positron emission tomography combined with computed tomography (^{18}F-FDG-PET/CT) or abdomen CT/chest CT/bone scintigraphy and brain CT or brain magnetic resonance imaging. Clinical mediastinal and hilar lymph node statuses were considered positive if the shorter axis was >10 mm.

The mean postoperative follow-up period for the surviving patients was 27 ± 18 months.

3. Histological diagnosis

Two pathologists (H.K. and M.T.) independently assessed hematoxylin and eosin-stained glass slides prepared from the resected lung cancer specimens to determine the adenocarcinoma subtype according to the IASLC/ATS/ERS criteria [12]. Disagreements on the individual pathological diagnosis of a case were resolved by the consensus achieved after a discussion between the two pathologists while viewing specimens under a double-headed microscope, as previously reported [13].

4. CEA measurement

The serum CEA level was measured using a “sandwich-type” immunoassay [14] with an acridinium ester-conjugated anti-CEA rabbit polyclonal antibody and a magnetic particle-bound anti-CEA murine monoclonal antibody on an automated chemiluminescence detection system (ADVIA Centaur CP Immunoassay System; Siemens Healthcare, Munich, Germany), according to the manufacturer's instructions. In this system, the range of detectable serum CEA was 0.5–100 ng/mL. Serum samples were collected from all patients within 1 month prior to lung surgery.

5. Statistical analysis

Values between two groups were compared using the non-parametric Mann–Whitney U test. Values between multiple groups were compared by the Kruskal–Wallis test. Multiple regression analysis was used to identify significant predictive factors for serum CEA levels. Disease-free survival (DFS) and overall survival (OS) after surgery were calculated using the Kaplan–Meier method, and differences in survival between the patient groups were identified using the log-rank test. Cox regression analysis was used to identify significant risk factors for postoperative DFS. A p value of <0.05 was considered statistically significant for all statistical tests.

6. Results

Characteristics of the included patients were shown in Table 1. The patients included 153 men and 154 women [age range, 22–88 years; mean $\pm$ standard deviation (SD), 69 ± 9 years]. Clinical (c-) stages were IA in 186 cases, IB in 93, IIA in 10, IIB in 10, IIIA in six, and IV in two. The two c-stage IV cases were patients with solitary brain metastasis who were simultaneously treated with lung resection. Because of the omission of lymph node dissection, mainly due to limited lung resection, information regarding the pathological (p-) N-stage could not be obtained in 67 cases. Sixty-six cases were excluded from the analyses of pathological staging because of the above stated reasons, with the exception of one case that was determined as p-stage IV due to pleural dissemination (p-M1a) found intraoperatively in spite of the lack of pathological information regarding regional lymph node status. The postoperative pathological stage was p-IA in 155 patients, p-IB in 41, p-IIA in 10, p-IIB in nine, p-IIIA in 23, and p-IV in three. Surgical methods were lobectomy in 203 cases, sublobar resection

Table 1
Characteristics of the included patients who underwent surgery for lung adenocarcinoma.

Factor		N (%)
Gender	Male	153 (50)
	Female	154 (50)
Age (years)	Mean $\pm$ SD	69 ± 9
	Range	22–88
Tumor size (mm)	Mean $\pm$ SD	29 ± 13
	Range	8–93
Clinical stage	IA	186 (61)
	IB	93 (30)
	IIA	10 (3)
	IIB	10 (3)
	IIIA	6 (2)
	IIIB	0
	IV	2 (1)
Surgery	Lobectomy	203 (66)
	Sublobar resection	102 (33)
	Pneumonectomy	2 (1)
Subtypes	AIS	20 (7)
	MIA	20 (7)
	LPA	41 (13)
	PPA	106 (35)
	APA	90 (29)
	IMA	3 (1)
	SPA	23 (7)
	MPA	4 (1)
Total		307 (100)

Abbreviations; SD=standard deviation, AIS=adenocarcinoma in situ, MIA=minimally invasive adenocarcinoma, LPA=lepidic predominant adenocarcinoma, PPA=papillary predominant adenocarcinoma, APA=acinar predominant adenocarcinoma, IMA=invasive mucinous adenocarcinoma, SPA=solid predominant adenocarcinoma, MPA=micropapillary predominant adenocarcinoma.