Usefulness of carcinoembryonic antigen in the diagnosis of small cell lung cancer combined with adenocarcinoma

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Advances in Clinical and Experimental Medicine, ISSN 1899-5276 (print), ISSN 2451-2680 (online) *Adv Clin Exp Med*. 2017;26(7):1091–1094

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Funding sources
None declared

Conflict of interest
None declared

Acknowledgment
This work was funded by Project 81202806 and 81303213 supported by the National Natural Science Foundation of China, Zhejiang Province Medical Science Fund Project of China (No.2010KYA035, No.2012KYB034).

Received on October 15, 2015
Revised on October 27, 2015
Accepted on October 26, 2016

Abstract

Background. Small cell lung cancer (SCLC) includes pure SCLC and SCLC combined with other pathologies (C-SCLC). C-SCLC accounts for about 28% of all SCLCs subjected to surgical resection, but only about 1–3% of C-SCLCs are detected by biopsy. Since less than 5% of SCLC patients are eligible for surgery, it is necessary to develop alternative methods for the detection of C-SCLC.

Objectives. We determined whether serum carcinoembryonic antigen (CEA) levels, which are usually elevated in lung adenocarcinomas, could be used to differentiate between pure SCLC and SCLC combined with adenocarcinoma.

Material and methods. We reviewed the records of 41 SCLC patients (35 with pure SCLC, 6 with C-SCLC) who underwent surgical resection between 2000 and 2014 in Zhejiang Cancer Hospital. Their preoperative serum CEA levels were noted, and the relationship between CEA level and the type of SCLC was analyzed.

Results. Serum CEA levels >6ng/mL were found more frequently in C-SCLC patients than in pure SCLC patients ($p = 0.031$). No such difference was observed when a CEA cut-off of 5ng/mL was used ($p = 0.316$).

Conclusions. A preoperative serum CEA of >6ng/mL may be used as a reference in the diagnosis of SCLC combined with adenocarcinoma.

Key words: diagnosis, small cell lung cancer (SCLC), carcinoembryonic antigen (CEA), adenocarcinoma

DOI
10.17219/acem/66372

Lung cancer is one of the most common malignant tumors and has the highest mortality rate of any cancer. Small cell lung cancer (SCLC) is a highly aggressive and lethal type of cancer in humans and accounts for approx. 13% of all cases of lung cancer.[1] SCLC is sensitive to chemotherapy and radiotherapy; however, long-term survival is low, and the majority of patients eventually develop progressive disease. Moreover, there is a high rate of relapse, even among patients who have achieved a complete response. Combined SCLC (C-SCLC) is a special histological type of SCLC, which presents different tumor molecular characteristics from pure SCLC.

Although the World Health Organization (WHO) considers C-SCLC to be a subset of SCLC, C-SCLCs can have many features of non-small cell lung cancer (NSCLC).[2] Recent research has shown that, although patients with C-SCLC might have a similar prognosis as those with pure SCLC, C-SCLC patients who undergo surgery have a better overall survival rate than pure SCLC patients who undergo surgery.[2,3] The treatment of C-SCLC can also be different from that of pure SCLC.[4]

Finding an appropriate method to detect and diagnose C-SCLC is difficult. It is known that serum carcinoembryonic antigen (CEA) is usually elevated in patients with lung adenocarcinoma.[2] However, at present, no study has examined serum tumor markers as a reference for diagnosing C-SCLC. To explore the possibility of using serum CEA as a supplementary diagnostic test for SCLC combined with adenocarcinoma, we retrospectively analyzed the preoperative serum CEA levels in 35 patients with pure SCLC and 6 patients with SCLC combined with adenocarcinoma. All patients had undergone surgery at Zhejiang Cancer Hospital (Hangzhou, China), and the surgical specimens of all patients had been examined.

Material and methods

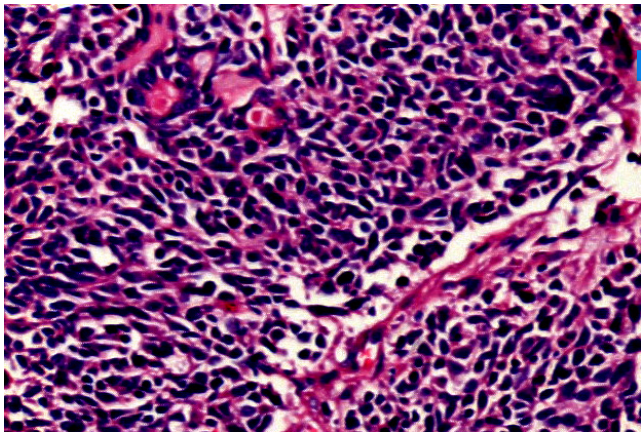
Patient characteristics

Our study involved 35 patients with pure SCLC and 6 consecutive patients with SCLC combined with adenocarcinoma (C-SCLC) who were admitted to Zhejiang Cancer Hospital between January 2000 and May 2014. This study was approved by the ethics committee of Zhejiang Cancer Hospital. SCLC staging was performed in all patients according to the 7th edition of the TNM classification for lung cancer. The preoperative serum CEA levels were retrospectively collected. In all patients, the histological diagnosis was based on the standard criteria defined in the WHO classification. Among the C-SCLC patients, 66.7% were men, 33.3% were aged >65 years, and 66.7% were heavy smokers. Two patients had stage IB disease, and 4 had stage IIIA disease. Two of the patients were non-smokers, and 4 were heavy smokers (Table 1, Fig. 1).

Table 1. Clinical characteristics of 35 patients with pure SCLC and 6 patients with SCLC combined with adenocarcinoma

Variables	Total	Pure SCLC n (%)	SCLC combined with adenocarcinoma n (%)	p-value
Age (years).				
<65	36	32 (91.4%)	4 (66.7%)	0.598
≥65	5	3 (8.6%)	2 (33.3%)	
Sex.				
female	7	5 (14.3%)	2 (33.3%)	0.567
male	34	30 (85.7%)	4 (66.7%)	
Smoking history.				
light	4	4 (11.4%)	0	0.635
mild	5	4 (11.4%)	0	
heavy	23	20 (57.1%)	4 (66.7%)	
never	9	7 (20.1%)	2 (33.3%)	
Pathological stages.				
I	11	9 (25.7%)	2 (33.3%)	0.522
II	8	8 (22.9%)	0	
III	22	18 (51.4%)	4 (66.7%)	
IV	0	0	0	

Fig. 1. Patient (70-year-old man) with stage IIIA pT2N2M0 SCLC combined with adenocarcinoma



Pathological result was detected using H&E staining, showing SCLC combined with adenocarcinoma cell lung cancer. ALK(D5F3)(-), ALK-NC(-), CK5/6(-), CK7(-), Napsin A(-), P63(-), TTF1(+). All images with original magnification ×200 and H&E stained unless otherwise indicated.

Statistical analysis

Two threshold values of CEA, 5ng/mL and 6ng/mL, were adopted to distinguish C-SCLC from pure SCLC. The data was analyzed using version 15.0 of the SPSS software package. The χ^2 test was used in univariate analyses, and corrections were done when there were less than 5 cases. Statistical significance was indicated at p-values of <0.05.

Results

Different Serum CEA levels between C-SCLC and pure SCLC patients

Most of our patients were men, older than 65 years, and had a history of heavy smoking. The clinical characteristics of the C-SCLC patients did not significantly differ from those of the SCLC patients. Preoperative serum CEA levels >6ng/mL were more frequently observed in C-SCLC patients than in pure SCLC patients (p = 0.031). No such difference was observed in the case of CEA levels >5ng/mL (p = 0.316; Table 2).

Table 2. Serum CEA level in pure SCLC patients and SCLC combined with adenocarcinoma patients

CEA (ng/mL)	Pure SCLC n (%)	SCLC combined with a denocarcinoma n (%)	p-value
≤5	27 (77.1%)	3 (50%)	
>5	8 (22.9%)	3 (50%)	0.316
≤6	32 (91.4%)	3 (50%)	
>6	3 (8.6%)	3 (50%)	0.031

Discussion

SCLC is a highly aggressive and lethal type of cancer in humans. Although there has been a modest, statistically significant improvement in 2- and 5-year survival rates over the last 30 years, the outcomes of SCLC remain extremely poor.[1] Chemotherapy is the cornerstone of therapy for SCLC. By 2002, the proportion of SCLC had decreased to approximately 12.95% of all lung cancers.[1,5] C-SCLC has been reported to account for 1–3.2% of all SCLC cases.[6,7] C-SCLC is defined by the WHO as SCLC combined with an additional component that consists of any of the histological types of NSCLC, usually adenocarcinoma, squamous cell carcinoma, or large cell carcinoma and less commonly spindle cell or giant cell carcinoma. In the case of large cellcarcinoma, an arbitrarily chosen cut-off of at least 10% large cell carcinoma is required for the diagnosis of C-SCLC.

Surgical specimens reflect the clinic pathological status, and the specimens of a high percentage of SCLC patients (28%) show an additional NSCLC component.[8] Due to the presence of crush artifacts and/or the limited availability of biopsy specimens, the possibility of detecting an NSCLC component in SCLC on histology is low. Thus, many cases of C-SCLC may be missed during the examination of biopsy specimens from SCLC patients. With improvements in diagnostic methods, more and more C-SCLC could be detected in recent years.[8] In our study, all SCLC patients underwent surgery before chemotherapy. All specimens in our study were surgical specimens, which are relatively rare and are very informative.

The 7th edition of the TNM classification has also been cited in the National Comprehensive Cancer Network (NCCN) guidelines for SCLC (2015 v. 1). T1–2N0M0 SCLC patients have been reported to account for less than 5% of all SCLC patients.[9] Among SCLC patients, only those with cancers classified as T1–2N0M0 are eligible for surgical treatment; in contrast, surgery may be used to treat NSCLC patients in stages IA, IB, IIA, IIB, and IIIA. Thus, few SCLC patients are eligible for surgery. Complete preoperative assessment is required before surgery for SCLC to exclude the presence of nodal involvement. In stage I SCLC, surgery always must be followed by adjuvant chemotherapy, while in stages II and III, surgery must be planned only in the context of clinical trials and after a pathologic response to the induction of chemoradiotherapy has been confirmed.[10] The incidence of brain metastasis can be reduced with prophylactic cranial irradiation.[11,12] It is difficult to diagnose C-SCLC by biopsy, and the rarity of patients with C-SCLC makes it difficult to determine the optimal management and biological characteristics of this tumor. Few studies have investigated C-SCLC, and more research should be conducted to identify the clinical features of these patients.[13]

Some studies have indicated that the clinical characteristics of C-SCLC patients do not significantly differ from those of pure SCLC patients.[6,8,14] Consistent with this, we found no significant differences in the clinical characteristics between SCLC and C-SCLC patients. Using genotypic and immunophenotypic analyses, Wagner et al. found that C-SCLC is biologically similar to SCLC.[14] However, the overall survival after surgery can differ between SCLC and C-SCLC patients.[2,3]

Serum tumor marker testing is a noninvasive, repeatable, and effective method for assisting the diagnosis of cancer. Serum CEA levels are invariably elevated in lung adenocarcinoma.[15,16] We, therefore, attempted to find a cut-off value of preoperative serum CEA level that would assist in the diagnosis of C-SCLC. As adenocarcinoma is a common additional component in C-SCLC, our research focused on evaluating the usefulness of preoperative serum CEA levels in the diagnosis of SCLC combined with adenocarcinoma.

Pretreatment CEA levels of 3–10 ng/mL have been reported in lung cancer.[15,17–19] In this study, a CEA cut-off of 5 ng/mL was not found to be useful for distinguishing SCLC combined with adenocarcinoma from pure SCLC. This may be because most of our patients had a history of cigarette smoking, and serum CEA levels are known to be elevated in smokers.[20–22] We found that a relatively higher threshold of 6 ng/mL CEA was useful for distinguishing SCLC combined with adenocarcinoma from pure SCLC.

Although the prognosis of C-SCLC is similar to that of pure SCLC, its sensitivity to chemoradiotherapy is lower than that of pure SCLC.[23] This phenomenon is attributable to the mixed NSCLC component in C-SCLC. The possibility of a tumor with combined pathologies should be considered in patients who are thought to have SCLC on the basis of limited biopsy materials, such as needle aspiration or bronchial biopsy specimens, or when the primary lesion is found to be peripherally located on chest radiography.[6] Our previous study has shown that epidermal growth factor receptor (EGFR) mutations may occur in C-SCLC, particularly when the "combined" component is adenocarcinoma.[13] More effective treatments (e.g., EGFR-tyrosine kinaseinhibitors) can be administered to patients who have SCLC combined with adenocarcinoma if a definite diagnosis is achieved.[4,24]

Conclusions

In conclusion, our retrospective study suggested a role for serum CEA level as a reference marker in the diagnosis of SCLC combined with adenocarcinoma. If SCLC patients have a serum CEA level higher than 6 ng/mL, they may have SCLC combined with adenocarcinoma and should be offered a further work-up (e.g., repeat or multi-point biopsy) in order to reach an accurate diagnosis. However, further prospective studies are required to support this conclusion.

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