

# Combined small cell lung carcinoma with pulmonary adenocarcinoma

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## Case report

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## Abstract

### Background

Combined SCLC is defined as SCLC combined with an additional component that consists of any of the histological types of non-SCLC, usually squamous cell carcinoma or large cell carcinoma. CSCLC contains adenocarcinoma is extremely rare and has been reported to account for less than 1–3% of CSCLC.

### Case presentation:

We report a case with a rare and surgically treated CSCLC with adenocarcinoma in an elderly and concerned with the clinical features of this disease. The patient has remained well for over 2 weeks after the treatment without any signs of disease recurrence.

### Conclusion

Combined small cell carcinoma is uncommon, but is nevertheless a well-described diagnostic category in lung cancers. To facilitate the preoperative diagnosis and avoid the misdiagnosis of such rare disease, more cases will need to be reported.

### Introduction

Combined small cell lung carcinoma (CSCLC) is defined by the World Health Organization (WHO) as small cell carcinoma combined with any non-small cell histologic type, including adenocarcinoma, squamous cell carcinoma, and large cell neuroendocrine carcinoma<sup>1</sup>. Only 13% of primary lung tumors are small cell lung cancer (SCLC). SCLC was first described by Barnard in 1926 as oat celled sarcoma which is the first statement of CSCLC in the world. CSCLC is rare in clinical patients, accounting for less than 1-3.2% of all SCLC<sup>2,3</sup>. We report a case with CSCLC and surgically treated CSCLC with adenocarcinoma in an elderly and concerned with the clinical features of this disease.

### Case Report

A 73-year-old man was admitted to our hospital for assessment of nodule that was detected on chest radiography during a routine health check. He had smoked one pack of cigarettes per day for the past 20 years and quit smoking for nine months. He denied the symptoms including the presence of chest pain, hoarseness, hemoptysis, cough and dyspnea. He had no risk factors for human immunodeficiency disease or other infections. Physical examination revealed normal breath sounds in both of the lung fields. Laboratory findings were within normal limits. His Pulmonary function tests and cardiovascular examination revealed normal performance. Plain and contrast-enhanced chest computed tomography (CT) (Figure A and B) showed obvious enhancement in soft tissue contained some calcified components, measuring 2.4 cm ×3.0 cm in size, in the lower lobe of the right lung. The bronchoscopy examination was done in patient but it showed nothing in trachea and bronchus. As diagnosis was not established through imaging, surgery was scheduled. The patient was subjected to lobectomy by utilizing a three-port video-assisted thoracic surgery (VATS). There was no invasion into the adjacent structures. Tissue of the mass was taken out with a biopsy forceps from the tumor for quick frozen pathology, which was pathologically diagnosed as combined small cell lung cancer with adenocarcinoma.

### Discussion

According to the 2004 WHO/International Association for the Study of Lung Cancer (IASLC) classification of lung and pleural tumors, CSCLC is defined as SCLC combined with one of the histological types of non-SCLC, usually squamous cell carcinoma or large cell carcinoma<sup>4,5</sup>. CSCLC contains adenocarcinoma is extremely rare and has been reported to account for less than 1–3% of CSCLC<sup>6</sup>. Only 15 cases including our patient of pulmonary SCLC combined with adenocarcinoma have been reported in 7 English literatures. As summarized in our Table, the male to female ratio was 4:1 and the mean age was 68 years (Table).

In our analysis, CSCLC is usually asymptomatic and may be diagnosed as an incidental finding and majority of male patients are smokers, and it illustrates the correlation between CSCLC and smoking. There was no pain or cough in our case caused by the lesion, but it was detected from the chest radiography during a routine health check. Because the tumor is rare, criteria for diagnosing CSCLC

radiologically do not exist. Chest radiographs are the most generally performed imaging study to evaluate the mass, but it may not be possible to distinguish CSCLC from pure SCLC. In our Table, seven tumors were located in the upper lobes and eight masses were located in the lower lobes showing from the contrast-enhanced chest CT.

Histopathologically, as seen in our case, the tumor lesion is composed of two completely different parts, which can be clearly defined under the microscope. In the SCLC part, the central component is mostly composed of small, uniform, poorly differentiated necrotic cancers (Figures C and D), while the other half is considered to be adenocarcinoma with papillary and acinar features. Immunohistochemically, in the pulmonary tumor, 75% of the small cell carcinoma cells strongly expressed TTF-1, vimentin and pancytokeratin, and 20% of the small cell carcinoma cells strongly expressed CD56, synaptophysin, and S100 protein<sup>7,8</sup>. As showed in Bai, et al<sup>7</sup> report, The components of SCLC are positive for synaptophysin (Syn), chromogranin A (CgA), and nerve cell adhesion molecule 1 (CD56), and have high proliferative activity by Ki-67 antigen immunostaining, while the adenocarcinoma area had low Ki-67 proliferation activity and was negative to others.

Clonality analysis of each component is also useful in determining the relationship between the different morphological patterns in CSCLC. In Wagner et al<sup>9</sup> research, using loss of heterozygosity (LOH) analysis included 3p and 17p in the separate components of lesion in each patient. Case 3 showed near-complete loss of 1 allele in the SCLC component and a greatly reduced amount of the same allele in the NSCLC component. In case 2 in our Table, LOH is demonstrated only in the SCLC component. Some researchers examined the point mutations in the p53 gene and LOH of chromosome 3p in each component. The results suggest that the small cell and squamous cell carcinoma components of CSCLC are clonally related, but that the adenocarcinoma component is derived from a separate clone<sup>10</sup>.

Although small cell lung cancer is highly sensitive to chemotherapy and radiotherapy, most patients will eventually develop multiple organs metastasis of lung cancer cells. Surgical resection is only performed in a limited number of patients with limited period. The combination of etoposide plus cisplatin has been considered as traditional first line treatment for SCLC<sup>11</sup>. With the advances in the diagnosis of lung cancer, the frequency of CSCLC has been raising in recent years. The role of surgery in the treatment of CSCLC is increasingly valued<sup>6</sup>. For patients with no metastasis to the lymph node, lobectomy with systemic hilar and mediastinal lymphadenectomy are preferred<sup>12</sup>. We can see from the Table, the surgery was performed in all patients with video-assisted thoracic surgery (VATS) in six cases or lobectomy by standard thoracotomy in nine patients. Almost all patients with small cell lung cancer have a tendency to spread throughout the body. Therefore, combined chemotherapy and chest radiotherapy are the main treatments for this disease<sup>13,14</sup>. In Table, four patients underwent chemotherapy and three of them got radiation therapy. In case 7, reported by Iezumi, et al.<sup>8</sup>, the patient received combined chemotherapy (cisplatin and irinotecan hydrochloride), but forearm metastasis recurred, and radiation therapy was performed on the affected area. Molecular targeted therapy has been developed using agents such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, which exerts antitumor activity in patients with adenocarcinoma with EGFR mutations<sup>15,16</sup>.

Some authors believe that pure and CSCLC have a similar clinical behavior with similar outcomes from surgery in limited stages of both conditions and some clinical data on characteristics and outcome of these patients have been published<sup>17-20</sup>. In one study, 5-year survival of patients with CSCLC was only 15.9% according to the higher ratio of extensive disease and the larger sample size (N = 114). They compared patients with CSCLC to a group of patients with pure SCLC and the data indicate that a similar prognosis of them. However, the rate of surgery for CSCLC was much higher compared with pure SCLC. Among patients with extensive disease who were not given surgery, that were given equivalent chemotherapy, CSCLC cases had a poorer overall survival (OS) than pure SCLC patients, whereas the prognosis of cases received surgery in the two groups was similar<sup>19</sup>. Hage *et al.*<sup>17</sup> also reported that surgical resection in selected patients with pretreatment clinical stage I combined and pure SCLC can be curative or offer long term survival. However, the OS of the patients with CSCLC was significantly higher than patients with pure SCLC in Babakoochi *et al* research<sup>20</sup>. They found there was a 100% 5-year survival of patients with stages 1 or 2 CSCLC and this is contrast to the Hage et al study before.

In conclusion, there are very few reports in the literature depicting the natural history of CSCLC in an adult in regard to its presentation, pathology and treatment. Since the shorter survival in extensive stage than the pure SCLC subtypes, early detection and surgery in early stage should be considered at the first place in CSCLC management. Surgical resection is performed in a limited number of patients which can be curative or offer long term survival in selected patients with CSCLC. To facilitate the preoperative diagnosis and avoid the misdiagnosis of such rare disease, more cases will need to be reported.

## Declarations

## Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## Availability of data and materials

All data for this study are publicly available and are ready for the public from database of hospital.

## Competing interests

The authors have no conflicts of interest to declare.

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## Consent for publish

All the authors consent to publish the paper.

## Authors' contributions

CS was involved in drafting the manuscript. GC designed and revised the manuscript. All authors have read and approved the final manuscript.

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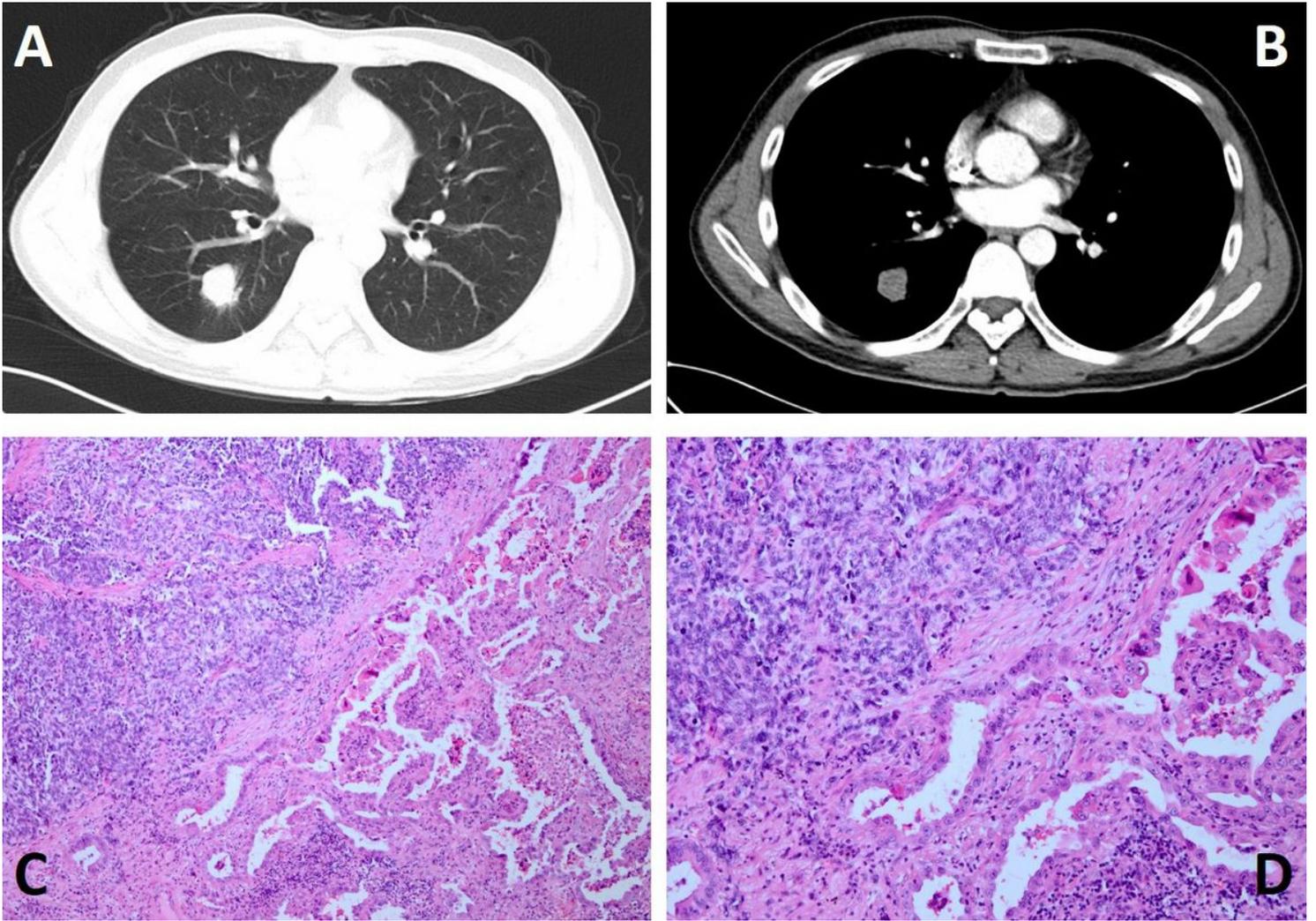
## Tables

### Table Clinicopathological features of the CSCLC

No	Age	Gender	Smoking	Location	Size (cm)	Treatment	Follow up*	Author
1	79	M	Yes	RLL	3.2x2.4x2.0	VATS	Alive 2 weeks	Ours
2	53	M	Yes	RUL	2.5	thoracotomy+CT+RT	Dead 23 months	Wagner <i>et al</i> <sup>9</sup>
3	77	M	Yes	LUL	2	thoracotomy+CT	Dead 16 months	Wagner <i>et al</i> <sup>9</sup>
4	72	F	None	LLL	1.6	thoracotomy+CT+RT	Dead 7 months	Wagner <i>et al</i> <sup>9</sup>
5	75	F	Not mention	RUL	Not mention	VATS	Alive 16.3 months	Babakoohi <i>et al</i> <sup>20</sup>
6	60	M	Yes	LLL	2.0x2.0x1.8	thoracotomy	Alive 12 months	Saito <i>et al</i> <sup>11</sup>
7	71	M	Yes	LLL	4	thoracotomy+CT+RT	Alive 36 months	Iezumi <i>et al</i> <sup>8</sup>
8	68	F	None	LLL	5	thoracotomy	Not mention	Bai <i>et al</i> <sup>7</sup>
9	68	M	Not mention	RLL	4	thoracotomy+RT	Dead 1.5 months	Murase <i>et al</i> <sup>10</sup>
10	71	M	Not mention	LUL	2.5	VATS	Alive 5 months	Murase <i>et al</i> <sup>10</sup>
11	73	M	Not mention	RLL	4	thoracotomy	Dead 10 days	Murase <i>et al</i> <sup>10</sup>
12	74	M	Yes	RLL	3.1	VATS	Not mention	Fukui <i>et al</i> <sup>19</sup>
13	62	F	None	LUL	3.1	VATS	Not mention	Fukui <i>et al</i> <sup>19</sup>
14	77	M	Yes	LUL	1.5	pneumonectomy	Not mention	Fukui <i>et al</i> <sup>19</sup>
15	76	M	Yes	RUL	2.8	VATS	Not mention	Fukui <i>et al</i> <sup>19</sup>

M= male; F: female; LUL: left upper lobe; LLL: left lower lobe; RUL: right upper lobe; RLL: right lower lobe; VATS= video-assisted thoracic surgery; CT=chemotherapy; RT=radiation therapy; \*: survival times are post-resection

## Figures



**Figure 1**

Chest contrast-enhanced CT and histological features and of the case. A and B: Contrast-enhanced CT scan showing a soft tissue, measuring 2.4 cm ×3.0 cm in size, in the lower lobe of the right lung. C and D: H&E staining reveals the tumor consisted of dual disparate components, which were intermingled in a combined pattern with a definite boundary at low magnification (C:X100 and D:X200).