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CASE REPORT

Rare Combined Small Cell Lung Carcinoma and Lung Squamous Cell Carcinoma Response to PD-1 Inhibitor as Third-Line Therapy: A Case Report

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Background: Combined small cell lung cancer (c-SCLC) is a relatively rare subtype of SCLC, especially when SCLC is initially diagnosed and recurrent lesions are non-small cell lung cancer (NSCLC). Moreover, SCLC combined lung squamous cell carcinoma (LUSC) has few been reported.

Case Presentation: Here, we report a 68-year-old man pathologically diagnosed as stage IV SCLC of right lung. With cisplatin and etoposide, the lesions were significantly reduced. It was not until three years later that a new lesion was found in his left lung, pathologically confirmed as LUSC. The patient was initiated with sintilimab based on high tumor mutational burden (TMB-H). Both lung tumors were stable, and PFS was 9.7 months.

Conclusion: This case provides a meaningful reference for the third-line treatment of SCLC combined LUCS patients. This case also provides valuable information on the response to PD-1 inhibition of patients with c-SCLC based on TMB-H and better understanding of PD-1 therapy applications in the future.

Keywords: c-SCLC, LUSC, PD-1 inhibitor, high tumor mutational burden

Introduction

Lung cancer is the most common cause of cancer deaths worldwide. Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are two histological subtypes of lung cancer. Treatment and prognosis of NSCLC and SCLC differ greatly due to their unique biology and genomic abnormalities. Combined SCLC (c-SCLC) is a relatively rare subtype of SCLC, defined as SCLC combined with any NSCLC elements, account for 2–28% of SCLC.[1] In particular, it is very rare when SCLC is initially diagnosed and the recurrent lesion is non-small cell lung cancer. It was reported that 314 SCLC patients were observed during the period 1976–1985. In 4 cases NSCLC was diagnosed after 3–11 years of observation.[2] In other words, the rate was only about 1.27%. In addition, the best treatment for c-SCLC, which is often referred to as SCLC, has not been fully established in China. However, this subset of patients is not small.

Although highly sensitive to chemotherapy or radiotherapy for extensive-stage SCLC (ES-SCLC), the median progress-free survival (mPFS) of first-line treatment is only 4.7–6.9 months.[3] The IMpower 133 trial is the first to demonstrate that the addition of atezolizumab to first-line chemotherapy prolongs median overall survival (mOS) and mPFS in patients with extensive stage SCLC.[4] However, second-line or third-line treatment for ES-SCLC is more limited

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and lacks treatment options. The emergence of immunotherapy provides a new treatment idea for ES-SCLC. How to improve the prognosis of this special patient population deserves clinicians' attention.

Here, we report for the first time a patient with newly diagnosed SCLC who progressed to c-SCLC, and PD-1 monotherapy as third-line therapy for c-SCLC achieved lasting clinical benefits. In addition, this report suggested that PD-1 inhibitor may be useful for patients with high tumor mutational burden (TMB-H) c-SCLC.

Case Descriptions

A 68-year-old man, with a smoking history for more than 30 years with 20 cigarettes/day, was admitted to our hospital with upper abdominal distension, black stools, blood in urine, dizziness and fatigue. The patient underwent surgery resection for mesenteric vascular embolism 9 years ago and recovered well. A computed tomography (CT) scan of the chest revealed a soft tissue mass of 52.0×31.0 mm in the right lower lobe, multiple pulmonary nodules, and enlarged mediastinal lymph nodes (Figure 1A). A CT-guided tumor biopsy was then performed, and the tumor was pathologically diagnosed as ES-SCLC of right lung (Figure 1B). The tumor cells were positive for synaptophysin, chromogranin A, thyroid transcription factor 1, and Ki-67 (50%), and negative for CK7, Napsin A, CK5/6, p40, p63, *EGFR* and *ALK*. In addition, laboratory examinations revealed elevations in the levels of carcinoembryonic antigen (CEA: 26.64 ng/mL), whereas no abnormalities were observed in carbohydrate antigen 19–9 (CA19-9), CA125, CA242, alpha-fetoprotein

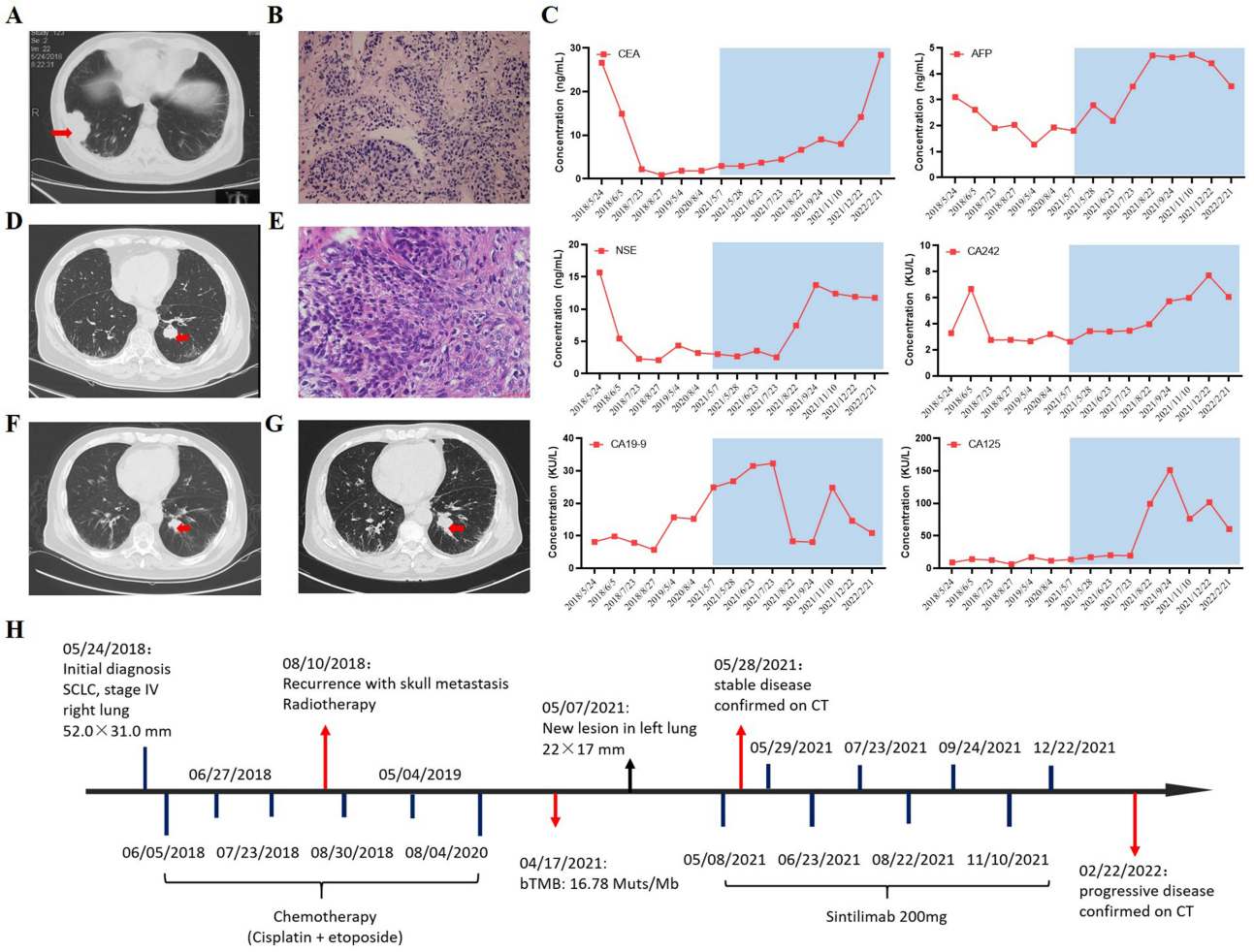

Figure 1 The treatment history of this patient. (**A**) Computed tomography (CT) from initial diagnosis on May 24, 2018 (Right lung: 52×31 mm). The red arrow indicates the tumors. (**B**) Hematoxylin-eosin staining of right lung (400 X). (**C**) Laboratory examinations of serum tumor marker. (**D**) CT images of new lesion in left lung on May 7, 2021 (Left lung: 22.0×17.0 mm; Right lung: 9.0×6.0 mm). The red arrow indicates the tumors. (**E**) Rebiopsy samples after chemotherapy resistance showed transformation to LUSC (400 X). (**F**) CT images of post PD-1 inhibition treatment on December 22, 2021 (Left lung: 18.0×16.8 mm; Right lung: 5.9×5.1 mm) and (**G**) recent re-examination on February 21, 2022 (Left lung: 34.0×20.0 mm; Right lung: 6.8×5.6 mm). The red arrow indicates the tumors. (**H**) Timeline of the clinical course in this patient.

(AFP) and neuron-specific enolase (NSE, Figure 1C). Cisplatin combined with etoposide was subsequently given. After 4 cycles of treatment, the maximum diameter of lung lesions decreased from 52 mm to 9 mm. However, there was a metastasis in the skull, indicating disease progression (PD). The metastases were treated with radiotherapy. Skull metastasis disappeared. Then the patient was given cisplatin and etoposide on May 4, 2019 and August 27, 2020, respectively. Until May 7, 2021, a new lesion appeared in the left lung (22.0×17.0 mm, Figure 1D). At this time, the size of the lesion in the right lung was 9.0×6.0 mm. The biopsy of left lung identified lung squamous cell carcinoma (LUSC) (Figure 1E).

To determine the potential therapeutic regimens, plasma next generation sequencing (NGS) using a panel of 733 cancer-related genes was performed which showed the *APC E1097*CDKN2A c.457+2T>A, NTRK1 D668A, TP53 H168R, V173M* and *R248W* mutations. The higher tumor mutation burden (TMB-H, 16.78 Muts/Mb) and microsatellite stable were identified. Informed consent was obtained from the patient. The patient was initiated with Sintilimab (200 mg on D1, every 3 weeks) based on TMB-H. After eight cycles treatment, the tumor lesion in the right lung significantly decreased (5.9×5.1 mm) and left lung remained stable (18.0×16.8 mm) (Figure 1F). Due to the Spring Festival, the patient did not receive treatment for two months. On February 21, 2022, the patient was re-examined, and CT showed slight enlargement of the right lung lesion (6.8×5.6 mm), but significant enlargement of the lung lesion on the left (34.0×20.0 mm), suggesting PD (Figure 1G and H). Finally, the PFS was 9.7 months.

Discussion

As far as we know, this is the first report of SCLC combined LUSC and response to PD-1 inhibitor as third-line therapy, making its prognosis better than conventional standard chemotherapy (median PFS: 0.7 months) or Anlotinib (median PFS: 4.1 months) which was recommended by CSCO guidelines as the only third-line drug in China (Table 1). Our case highlights the importance of repeated biopsy to manage disease progression and TMB as a potential biomarker for c-SCLC immunotherapy.

Although SCLC is highly sensitive to chemotherapy and radiotherapy, and the mOS for ES-SCLC patients is only 8–13 months.[10] However, the current research on c-SCLC is relatively limited, and the clinical standardization of c-SCLC is lacking, because the previous studies mostly treated the combined and simple SCLC as a whole. However, the survival

Table 1 The Previous Clinical Trials of Third-Line Treatment for SCLC

Trial	Patients	Treatment Settings	Primary Outcome
NCT03059797[5]	SCLC	Anlotinib vs Placebo	**mPFS** Anlotinib vs placebo: 4.1 vs 0.7 months; HR 0.19, p < 0.0001. **mOS** Anlotinib vs placebo: 7.3 vs 4.9 months; HR 0.53, p = 0.0029.
CheckMate 032[6]	SCLC	Nivolumab vs Nivolumab + Ipilimumab	**ORR** Nivolumab vs Nivolumab + Ipilimumab: 11.6% vs 21.9%; p=0.03. **mPFS** Nivolumab vs Nivolumab + Ipilimumab: 1.4 vs 1.5 months; **mOS** Nivolumab vs Nivolumab + Ipilimumab: 5.7 vs 4.7 months;
KEYNOTE-028 and KEYNOTE-158 studies[7]	SCLC	Pembrolizumab	**ORR**: 19.3%;
TRINITY study[8]	DLL3-expressing SCLC	Rovalpituzumab Tesirine	**ORR** All vs DLL3-high vs DLL3-positive:12.4% vs 14.3% vs 13.2%; **mOS** All vs DLL3-high vs DLL3-positive: 5.6 vs 5.7 vs 5.8 months;
Hanaoka M, et al study[9]	SCLC	Amrubicin	**ORR**: 27.8%; **DCR**: 66.7%; **mPFS**: 2.9 months

difference between c-SCLC and SCLC has been controversial,[11–13] possibly because some studies refer to SCLC as pure SCLC or confuse SCLC with c-SCLC. However, it is clear that there are differences between c-SCLC and SCLC in many clinicopathological features such as race, sex, T stage, N stage, surgery, bone, brain, and liver metastases.[14] In addition, c-SCLC is more heterogeneous, which may lead to enhanced metastatic capacity.[15] More important, according to the National Comprehensive Cancer Network (NCCN) SCLC guidelines (3rd edition, 2017), c-SCLC should be treated differently from pure SCLC because it contains some NSCLC components. Therefore, c-SCLC should not be completely equivalent to pure SCLC. Due to the rarity of c-SCLC in clinical practice, it is difficult to study as many c-SCLC patients as pure SCLC patients. But we would very much like to have a large clinical research center that can initiate such a study, even if it is a multicenter study. In our case, c-SCLC was treated with PD-1 inhibitors for third-line PFS for 9.7 months. More importantly, the OS of this patient was more than 45.3 months.

Circulation tumor DNA (ctDNA) is degraded DNA fragments released by tumor cells into the contaminated blood. Large numbers of evidence supports that ctDNA as a reliable alternative to tissue biopsy, providing a viable method to predict treatment response or monitor drug resistance.[16,17] TMB, defined as the total number of somatic/acquired mutations per coding area of a tumor genome (Mut/Mb), is the second tumor-agnostic biomarker approved by the US Food and Drug Administration (FDA) on the basis of its clinically significant objective response rate.[18] High TMB (TMB-H), which represents genomic instability, has the potential to induce a larger number of neoantigen production and further immunogenicity improvement.[19] However, due to the heterogeneity of tumors, the low accessibility of specimens, and the requirement of tissue NGS for specimen quality control, the use of ctDNA to measure TMB (namely, blood TMB [bTMB]) has attracted extensive attention as a non-invasive method to guide immune checkpoint blockades (ICBs) treatment.[20] A series of subsequent studies also confirmed bTMB as a feasible predictor of OS, PFS, and ORR after anti-PD-(L)1 therapies in patients with lung cancer.[21] In our case, the patient, who had progressed after previous treatment and had no satisfactory alternative, received immunotherapy based on TMB-H and achieved a significant reduction in tumor volume, suggesting that TMB may be a beneficial biomarker for c-SCLC undergoing immunotherapy.

In conclusion, we report for the first time a case of SCLC combined with LUSC and response to PD-1 inhibitor. Re-biopsy should be considered when dealing with resistance, and frequent monitoring may be needed.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of The Affiliated Haici Hospital of Qingdao University.

Consent for Publication

The patient provided written informed consent for the case details to be published.

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Disclosure

Zhisheng Liu and Junling Zhang are co-first authors for this study. Junling Zhang and Mengli Huang are employees of 3D Medicines Inc. The authors report no other conflicts of interest in this work.

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