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CASE SERIES

Extensive Stage Small-Cell Lung Cancer with Cystic Brain Metastases: A Report of Two Cases

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Objective: Cystic brain metastases (BMs) are rare in small cell lung cancer (SCLC), and there are limited data on the treatment and prognosis of cystic BMs. Whole brain radiotherapy has been the mainstay for BMs since several years. Immune checkpoint inhibitors in extensive stage small cell lung cancer (ES-SCLC) have been shown to be suitable for patients who experienced better overall survival and progress-free survival and have been approved as the first-line treatment for ES-SCLC. In this report, we described two ES-SCLC patients developed cystic BMs after immunotherapy, after which the patients continued to treat the primary lesion with immune checkpoint inhibitors and the cystic BMs with radiotherapy.

Case Description: Two male patients were diagnosed with ES-SCLC at the first admission and were subsequently treated with immunotherapy plus platinum therapy, during which cystic BMs developed. One patient received whole brain radiotherapy and the other received whole brain radiotherapy and Gamma knife radiosurgery (GKRS). Immunotherapy was continued after the brain lesions were controlled. It has been 33 months since the first patient was diagnosed and is now in stable condition. The other patient achieved an overall survival of 30 months.

Conclusion: This report describes two patients with cystic brain metastases in ES-SCLC. Whole brain radiotherapy has a good effect on local control of cystic brain metastases in small cell lung cancer and can significantly improve the symptoms of patients. At the same time, we treat immunotherapy as the first-line treatment, and then perform cross-immunotherapy after disease progression, combined with anti-vascular targeting drugs. The patient did not develop severe iRAEs.

Keywords: ES-SCLC, immunotherapy, cystic BMs, cross-line immunotherapy

Introduction

About 14–15% of all the lung cancer cases account for small cell lung cancer (SCLC). SCLC is characterized by high malignancy and rank first in cancer-related mortality.[1] Almost 80–85% of patients with SCLC are at an advanced stage, and approximately 10% of patients with SCLC are diagnosed with brain metastases (BMs) at the first visit, giving a median overall survival (OS) of 4.9 months due to limited treatment options.[2] Most of the metastatic brain lesions are solid rather than cystic.[3] In recent years, with in-depth research at the genetic level, targeted therapy and immunotherapy drugs, such immune checkpoint inhibitors (ICIs), have been increasingly applied for treating unresectable tumors. With the addition of immunotherapy, there has been a modest improvement in OS and PFS for patients with ES-SCLC.[4] The representative immunosuppressive checkpoint programmed cell protein (PD-1) programmed death ligand-1 (PD-L1) inhibitors activate host immunity to eliminate tumor cells by blocking the binding of checkpoints and ligands.[5] However, due to the highly malignant nature of SCLC, disease progression is inevitable. Several studies have reported that treatment with ICIs as a follow-up to disease progression continues to allow patients to benefit from immunotherapy.

Cystic BMs are defined as a cystic volume greater than 50% of the total volume. The mechanism of cystic BM development remains unclear. Cystic mass may be caused by fluid accumulation due to the breakdown of the blood–brain barrier.[6–8] Nearly all cystic BMs are characterized by large volumes. In recent years, with the introduction of the therapeutic concept of precision therapy, stereotactic radiosurgery (SRS) has replaced whole brain radiotherapy (WBRT) and gradually

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become the main treatment for BMs. However, for cystic BMs, WBRT remains the most important treatment.[9] When the large tumor size interferes with radiosurgery, stereotactic aspiration of the metastases should be considered to reduce the target volume, reduce the chance of radiation-induced necrosis, and provide symptomatic relief from a space-occupying effect.[10–12] Stereotactic cyst aspiration is a minimally invasive method that is not affected by the location of lesions in the brain and can immediately reduce neurological symptoms. Cyst aspiration also reduces tumor volume before radiotherapy to meet the requirements of Gamma knife radiosurgery (GKRS). Some studies suggest that GKRS combined with radiocyst aspiration is more effective than WBRT in the treatment of cystic brain metastases. However, the local control rate of GKRS was found to be worse than that of WBRT in another study.[3]

Case presentation

Case 1

A 66-year-old male was admitted to our hospital due to dyspnea and cough in January 2021. He had no smoking history, and no family history of hereditary disease. Enhanced chest computed tomography (CT) showed a mass in the hilum of the right lung and multiple nodules in the lower right lung. Lymph node metastasis in the right hilar and mediastinum and right supraclavicular fossa (Figure 1), with a high metabolic activity, was noted. Histopathology and immunohistochemistry of biopsied tissues through bronchoscopy suggested CD56+, chromogranin A (CGA+), CKpan+, Ki-67 (90%), leukocyte common antigen A (LCA-), Syn+, and thyroid transcription factor (TTF-1+) (Figure 2). Magnetic resonance imaging (MRI) of the brain and bone showed no metastases. ES-SCLC was eventually confirmed based on the pathological results and imaging scans. The patient initially received traditional chemotherapy including etoposide + cisplatin (EP) for one cycle, followed durvalumab in the second cycle. He received combined treatment for 6 cycles and showed a good response with slight gastrointestinal discomfort (Figure 1B). During the treatment, imaging and blood examinations were performed every 3 weeks.

In November 2021, the patient experienced speech impairment and motor apraxia of the fingers. After admission, MRI revealed an occupation in the left parietal lobe, which showed hypo-intensity in T1-weighted images, hyperintensity

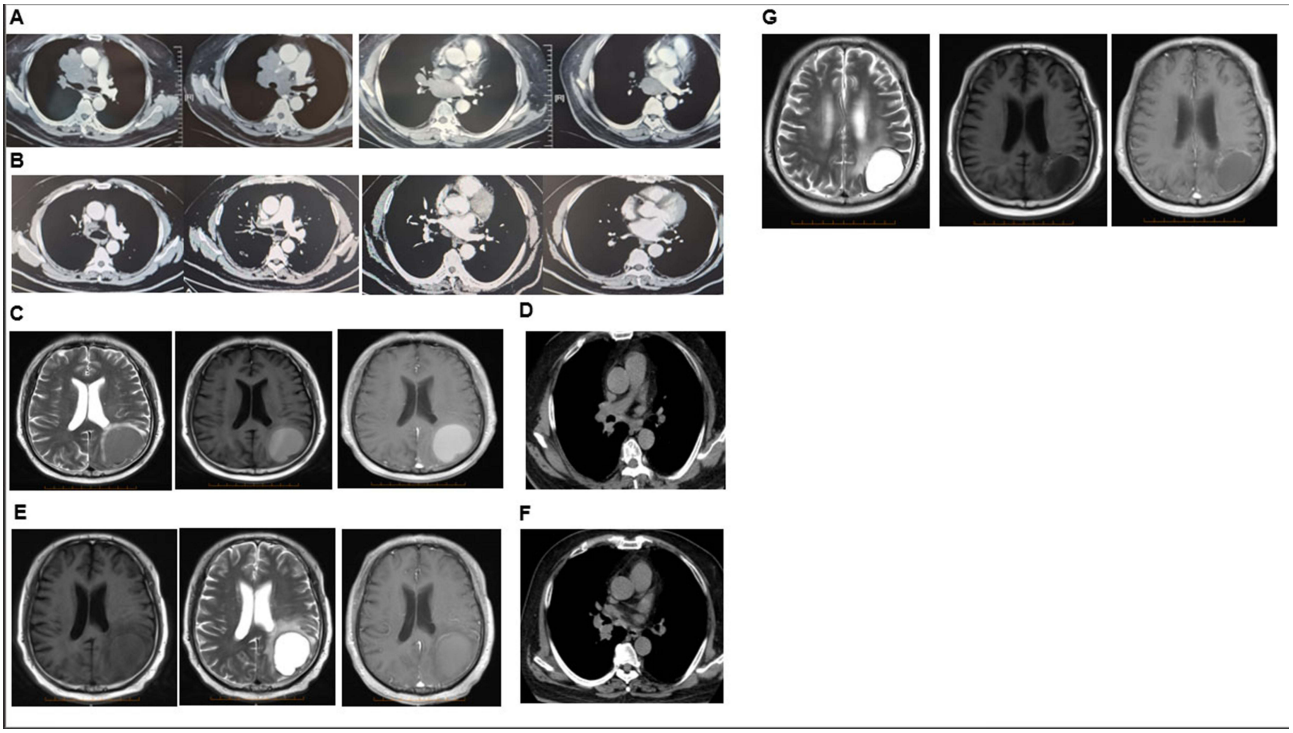

Figure 1 Baseline before immunotherapy. (**A**) 2 cycles after immunotherapy. (**B**) November 2021, cystic brain metastasis. (**C**) February 2022, 3 months after cystic brain metastasis. (**D**) February 2022, chest CT after radiotherapy for brain lesions. (**E**) May 2022, chest CT of recurrence of the right hilar of the right lung nodules. (**F**) November 2022, 1 year after cystic brain metastasis. (**G**).

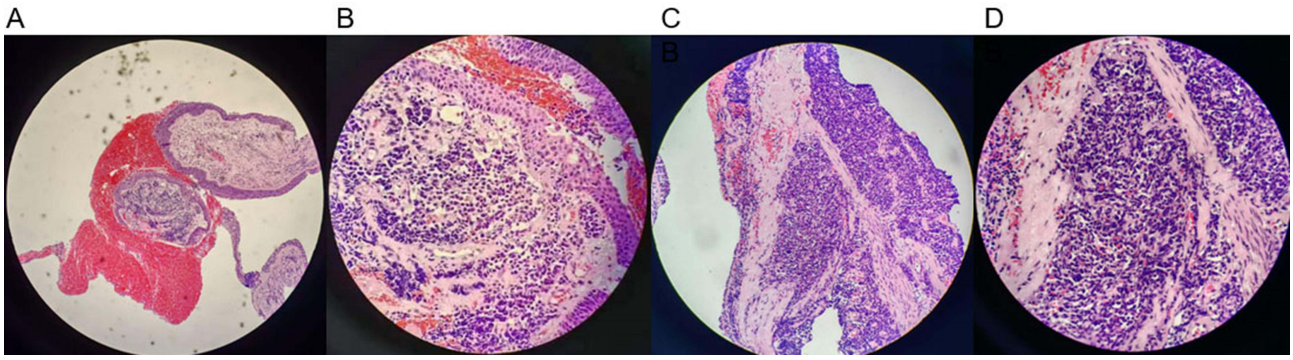

Figure 2 HE staining of primary lesion (ES-SCLC) in the first patient (**A**–**D**).

in T2-weighted images, and no enhancement (Figure 1C). After discussion, cystic BMs were considered. WBRT was suggested sequentially. After radiotherapy, the patient's speech function was partially restored. In February 2022 (Figure 1D), the patient underwent a chest CT and there was no significant change in disease compared to previous reports. He was given anlotinib in combination with durvalumab.

However, after 3 months, the patient' speech and limb dysfunction were significantly aggravated, and MRI showed a worsened peripheral edema (Figure 1E). CT suggested recurrence of right hilar nodules (Figure 1F). Considering the status of the patient, he received combined treatment including EP, bevacizumab, and durvalumab. After 2 cycles, MRI showed a decrease in the intracranial edema, and the right hilar nodule was markedly reduced. Prior to the completion of this report, it has been 33 months since diagnosis for the patient, and the most recent imaging showed that the patient's condition was stable (Figure 1G).

Case 2

On 14 March 2020, a 64-year-old male with a smoking history of 40 years presented with blurred vision. His father had died of bowel cancer and his brother had died of gastric cancer. A CT scan showed an abnormal mass in the lower lobe of the left lung. The patient presented with pleural effusion, which was extracted for cytological studies, and tumor cells were found (Figure 3). Lung aspiration of the pathological tissue suggested SCLC. Eventually, the patient was diagnosed with ES-SCLC with pleural effusion (Figure 4). Scans of the brain and full-body showed no abnormalities. The first-line regimen for this patient was EP + tislelizumab from 3 May 2020 to 21 July 2020 for 5 cycles. The patient's response was assessed as a partial response (PR) after 4 treatment cycles (Figure 3B and C).

On 28 March 2021, the patient was admitted to our hospital for routine examination, MRI revealed multiple metastases in the brain and the largest one was sized 5.5 × 4.1 cm in the left cerebellar hemisphere. Most of masses were cystic. Thus, the patient developed cystic BMs after 13 treatment cycles (Figure 3D). He received WBRT in combination with mannitol to reduce cerebral edema. After radiotherapy, a CT scan showed low left hemisphere density. The patient underwent CT scan in April and the lung lesions were stable (Figure 3E). This patient then received GKRS supplemental therapy for 3 small brain lesions on 10 May 2021 (Figure 3F). During the course of radiotherapy, the patient had a relatively severe rash reaction, which was relieved after the end of radiotherapy through dermatology consultation. In addition, the patient also had mild nausea, vomiting and other adverse reactions. The patient simultaneously received EP + tislelizumab as crossline immunotherapy. After GKRS, MRI revealed narrowed brain lesions and partial remission in some areas. Subsequently, the patient was switched to anlotinib in combination with tislelizumab due to a poor physical status and severe hypertension.

He was admitted to our hospital on 1 March 2022 for increased weakness in the lower extremities. Compared to the MRI on 5 November 2021, the patient's brain lesions showed no significant changes, and a full-body bone scan showed multiple metastases in the cervical and thoracic vertebrae. The patient stopped receiving immunotherapy (Figure 3G). He died in September 2022.

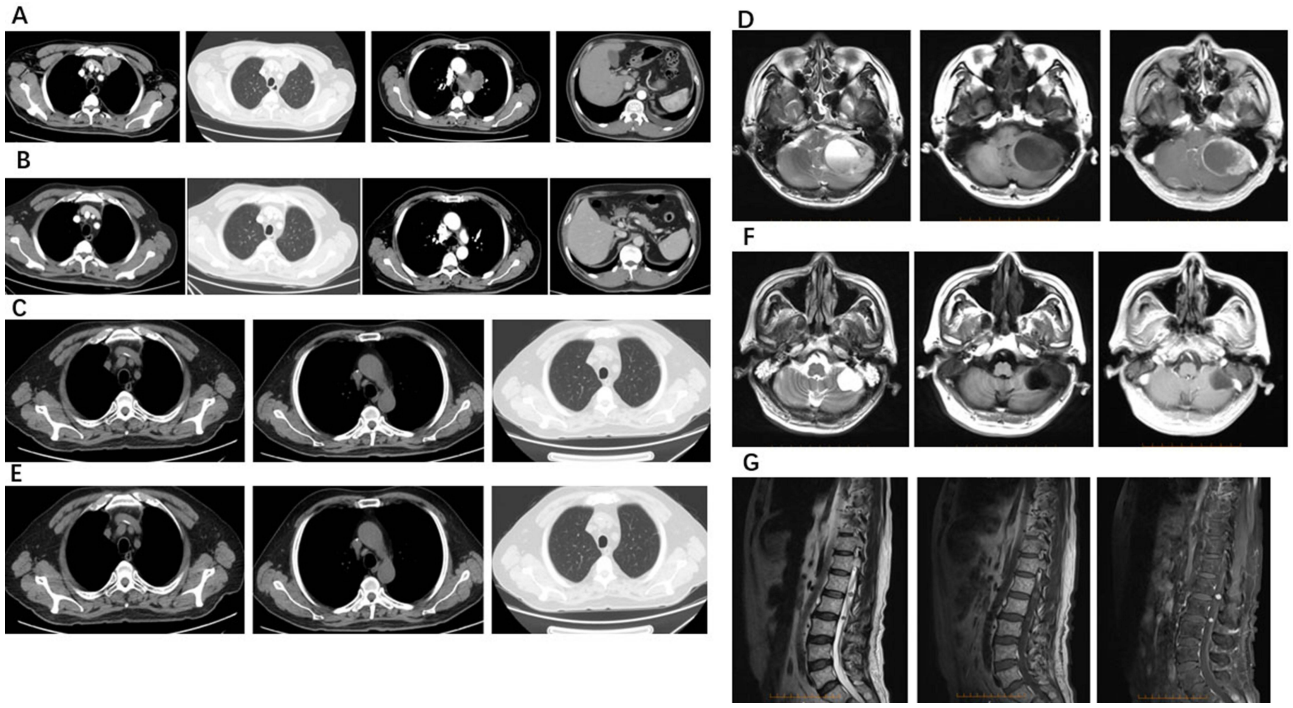

Figure 3 Baseline before immunotherapy. (**A**) 4 cycles after immunotherapy. (**B**) February 2021, chest CT before cystic brain metastasis. (**C**) March 2021, cystic brain metastasis. (**D**) April 2021, chest CT SD. (**E**) September 2021; 6 months after cystic brain metastases occurred. (**F**) March 2022, spinal metastasis. (**G**).

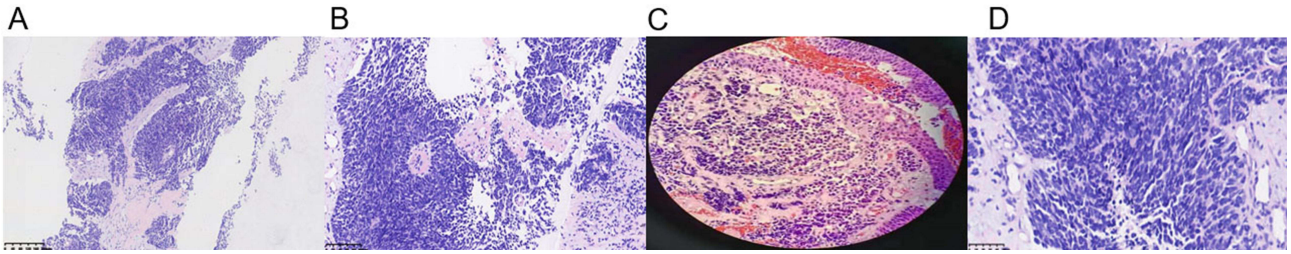

Figure 4 HE staining of primary lesion (ES-SCLC0 in the second patient (**A**–**D**).

Discussion

ES-SCLC is associated with high rates of malignancy, distant metastasis, and local recurrence. With platinum-based therapy, initial response rates were as high as 60–65%; progression-free survival (PFS) was 4.3–5.6 months.[13] With the advent of immunotherapy, IMpower133 and CASPIAN trials have shown that regardless of the PD-L1 expression, patients would benefit from ICIs.[14,15] The US Food and Drug Administration has approved atezolizumab or durvalumab in combination with platinum-based therapy as first-line treatment options for ES-SCLC. Topotecan is currently approved as the second-line standard treatment for recurrent SCLC.[16] With benefits of immunotherapy as the first-line treatment in ES-SCLC, studies, such as CheckMate 451,[17] CheckMate 331,[18] IFCT-1603,[19] have evaluated the efficacy and safety of ICIs as a second-line or late-stage treatment of platinum-based chemotherapy. Regrettably, the results suggest that ICIs as a second-line treatment cannot provide additional survival benefits to patients.

Compared with solid BMs, cystic BMs are less common, accounting for 1.7–18.8% of all metastatic brain tumors. Patients with lung and breast cancers have been particularly reported to develop cystic BMs.[3,20] The occurrence of cystic BMs is higher in lung cancer with genetic mutations, especially non-small cell lung cancer (NSCLC) carrying anaplastic lymphoma kinase (ALK) rearrangement or EGFR mutations.[20] It is speculated that tumors that respond well to targeted drugs are more likely to cause cystic degeneration of BMs.[7,21] Few studies have reported SCLCs with cystic BMs.[22] Poor

clinical outcomes and lack of clear clinical data are a challenge in the treatment of BMs.[23] Cystic BMs are characterized by large size, and elimination of cysts is critical during treatment.[24] A cyst aspiration technique can help reduce the cyst size.[6,25] GKRS, a surgery with minimal invasion and trauma, can reduce the incidence of related tumors and has a good local tumor control rate. GKRS is widely used, but local control is poor when applied to cystic BMs,[3,5,6] which may be attributed to the radiation resistance of the cystic components. Therefore, WBRT is currently preferred for the treatment of cystic BMs. In a study,[20] 288 patients were diagnosed with solid BMs and 33 with cystic BMs, it was found that among patients with adenocarcinoma, the incidence of cystic BMs in EGFR mutated NSCLC was 80.0% and that in ALK positive NSCLC was 20.0%. Comparing with solid BMs, patients with cystic BMs were more likely to benefit from targeted drugs. This study further showed that cystic BMs were prone to occur in NSCLC patients with genetic mutations, while NSCLC patients who respond well to targeted therapies were more likely to develop cystic BMs, this study suggests that cystic BMs are not necessarily a poor prognostic factor. In addition, when patients received chemotherapy, patients with cystic BMs had shorter PFS than patients with solid BMs. Cystic BMs cannot be controlled after radiotherapy, which has been verified in other studies. However, the number of cases included in this study is too small, and more conclusions need to be further confirmed.

In our cases, although one patient died, there are many experiences worth considering. We found that both cases had the following similarities: advanced stage at initial diagnosis; received immunotherapy and chemotherapy as first-line therapy; cystic BMs occurred during first-line treatment; BMs were treated with radiotherapy; none of them developed significant immune-related adverse effects (irAEs) during treatment; and the effect of their treatment on quality of life was minimal. The first patient received immunotherapy after diagnosis, developed cystic BMs 9 months later. The other patient received immunotherapy after diagnosis of ES-SCLC developed cystic BMs 1 year later, but the lung lesions were stable We believed that the patients will benefit from immunotherapy. Therefore, even if patients developed BMs, considering their condition, immunotherapy was administered.

Serplulimab (HLX10) is a novel humanized monoclonal anti-PD-1 antibody that was studied in the ASTRUM-005 study. Serplulimab was shown to provide survival benefits to patients with ES-SCLC and significantly prolong OS of those treated with a combination of serplulimab plus chemotherapy relative to chemotherapy alone (15.4 vs. 10.9 months; hazard ratio [HR], 0.63, 95% confidence interval [CI], 0.49–0.82; $P < 0.001$). However, it is worth noting that 24.1% of patients with ES-SCLC in the study were treated with serplulimab + carboplatin + etoposide therapy and continued treatment immunotherapy after disease progression, thereby receiving crossline immunotherapy.[26,27] The final outcome was that serplulimab could benefit patients with SCLC, but the additional benefit of crossline immunotherapy was not clear. In another study, a patient was diagnosed with ES-SCLC at the first visit, with a disease course of up to 7 years, and PFS was maintained for 22 months after anlotinib and carilizumab treatment.[28] Therefore, despite recurrence of lung lesions, the patient was judged to continue to benefit from immunotherapy. Thereafter, a combined regimen of penpulimab and anlotinib was given. The efficacy was evaluated as PR after 4 cycles of combined treatment, and there were no further adverse reactions. This case demonstrated the effectiveness of ICIs in immune reactivation. In a retrospective analysis of 17 patients with advanced NSCLC who were re-stimulated with different PD-1/PD-L1 inhibitors, 10 (58.8%) achieved PR or stable disease.

In recent years, data on the safety and efficacy of restarting ICI after immunotherapy have been interrupted by the presence of many irAEs.[29] A retrospective analysis concluded that it was relatively safe to continue or rechallenge patients with advanced cancers on immunotherapy-based regimens after the development of certain grade ≥2 irAEs, except for cardiac, neurological, or any grade 4 irAEs.[30] Another cohort study analyzing irAEs after ICI reactivation showed a recurrence rate of 28.8% (95% CI, 24.8–33.1).[31] No irAEs were more severe than initial irAEs, and a delay in irAEs onset compared to initial treatment (9.15 weeks vs 15 weeks $P = 0.04$) was noted. Furthermore, it was confirmed that patients who suspended the initial ICI treatment due to irAEs could tolerate ICI reactivation, and OS could be improved ($P = 0.025$).[32] In a cohort study of 144 patients, after stopping the first course of ICI, PD-1 or PD-L1 inhibitor was used for ICI retreatment. The median OS of retreatment was 1.5 years, and the median OS of patients who stopped the first course of ICI due to immunotherapy toxicity was better than that of patients who stopped due to disease progression.

The occurrence and severity of irAEs could not be used as indicators to predict whether patients benefit from ICI reactivation. Some studies have pointed out that the therapeutic effect of ICI varies from patient to patient. Currently, a specific influencing factor is the patient's Easter Cooperative Oncology Group Performance Status (ECOG PS) score.[33]

Multivariate analysis showed that an ECOG PS score of ≥2 (HR, 2.38; 95% CI, 1.03–5.52; P = 0.043) was negatively correlated with PFS. The ECOG PS score could be used as factor to evaluate whether patients should accept ICI rechallenge.

Conclusions

In summary, this report describes two patients with ES-SCLC who developed cystic BMs. The occurrence of cystic BMs is exceedingly rare, especially in SCLC, and the treatment of cystic BMs remains controversial. We treated the patients with immunotherapy as first-line and with crossline immunotherapy after disease progression, combined with anti-vascular targeting drugs. The patients did not develop severe irAEs. There are still many deficiencies in the treatment of cystic BMs and the evaluation of prognoses. Although crossline immunotherapy has been reported in several studies, there is a lack of large-scale clinical studies to confirm its safety and efficacy in ES-SCLC. Relevant clinical trials to obtain more scientific and rigorous data to verify these findings are warranted in the future.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for Publication

The authors have obtained informed consent from the patients for publication of the case details and any accompanying images, and the ethics committee of The General Hospital of Northern Theater Command approved this consent process and the publication of case details.

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Disclosure

The authors report no conflicts of interest in this work.

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