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Treatment of Brain Metastasis of Small Cell Lung Cancer with PD-1 Inhibitor: A Case Report

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Abstract

PD-L1 (Programmed Cell Death Protein L1) inhibitor has been used in the first-line treatment of extensive small cell lung cancer, but its prognosis is still poor and its survival time is short, especially in patients with brain metastasis. The effect of PD-1 inhibitor is not satisfactory as well. PD-1 (Programmed Cell Death Protein 1) inhibitors are less effective and used in the third-line treatment, and patients only experience short PSF benefit. Herein, we report a unique case of a patient with brain and adrenal metastases of small cell lung cancer for whom brain metastases partially disappeared, efficacy evaluation at 25 months follow - up PR, quality of life was good, and no significant adverse effects were observed after receiving comprehensive treatment with PD-1 inhibitor Toripalimab.

Keywords: small cell lung cancer, PD-1 inhibitor, Toripalimab

1. Case Report

A 72-year-old male patient, during physical examination in April 2018 right lung mass and soft tissue mass in the anterior segment of the upper lobe of the right lung were found, which considered as lung cancer, mediastinal lymph node enlargement were found, considered as metastasis. Bilateral supraclavicular fossa multiple enlarged lymph nodes, bilateral supraclavicular pathological punctures are suggestive of poorly differentiated carcinoma, lung needle biopsy, pathological returns: consider poorly differentiated carcinoma. A 2-cycle TC regimen (albumin bound paclitaxel 400mg D_1 + carboplatin 600mg D_2) chemotherapy was administered since 23-sep-2019, after which radiotherapy was administered. At the time of radiotherapy, GTVnd included double supraclavicular, bilateral cervical region IV, region III and left cervical region II with multiple enlarged lymph nodes, GTVnd with an external expansion of 0.6 cm was CTVnd, GTV included the left upper lobe nodule, GTV with an external expansion of 0.6 cm was CTV, CTVnd and CTV with an external expansion of 0.5 cm were PTVnd and PTV, respectively, and the prescribed dose given was 66 Gy / 30 F, and the efficacy after the end of radiotherapy was evaluated as PR.

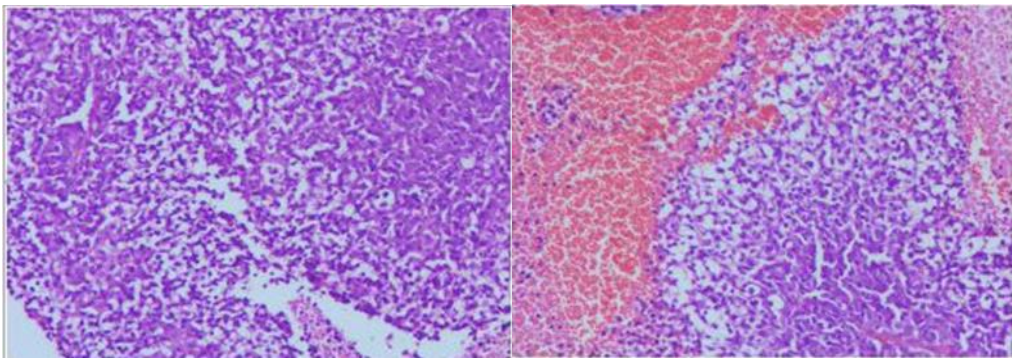

Figure 1. Pathological picture of intracranial metastatic foci (×100)

The patient had visual field defect in September 2019, head MRI tips: left occipital lobe signal abnormality, consider metastases, in October 2019 found left adrenal metastasis. Intracranial tumor resection was performed on 19-dec-2019 and postoperative pathological results were: small cell carcinoma (Fig.1). Immunohistochemical staining: CKpan(+), TTF-1(+), Syn(-),CgA(-), P63(-), LCA(-), Ki-67(80%+), CD56(+), CK5/6(-), NapsinA(-), CK7(-), P40(-).

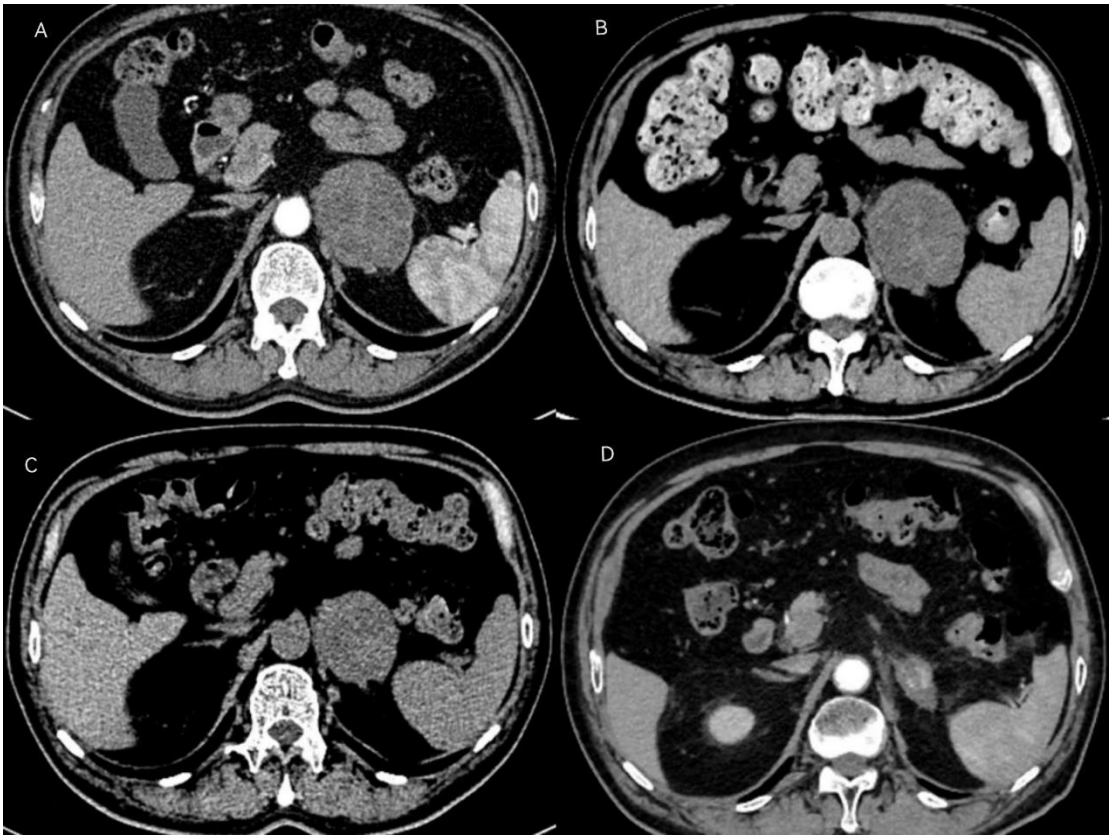

Figure 2. A-D Adrenal metastases before treatment (67mm×56mm×47mm), 1 month after treatment (70mm×58mm×61mm), 3 months after treatment (60mm×52mm×47mm) and 2022-4-11CT (33mm×21mm×18mm)

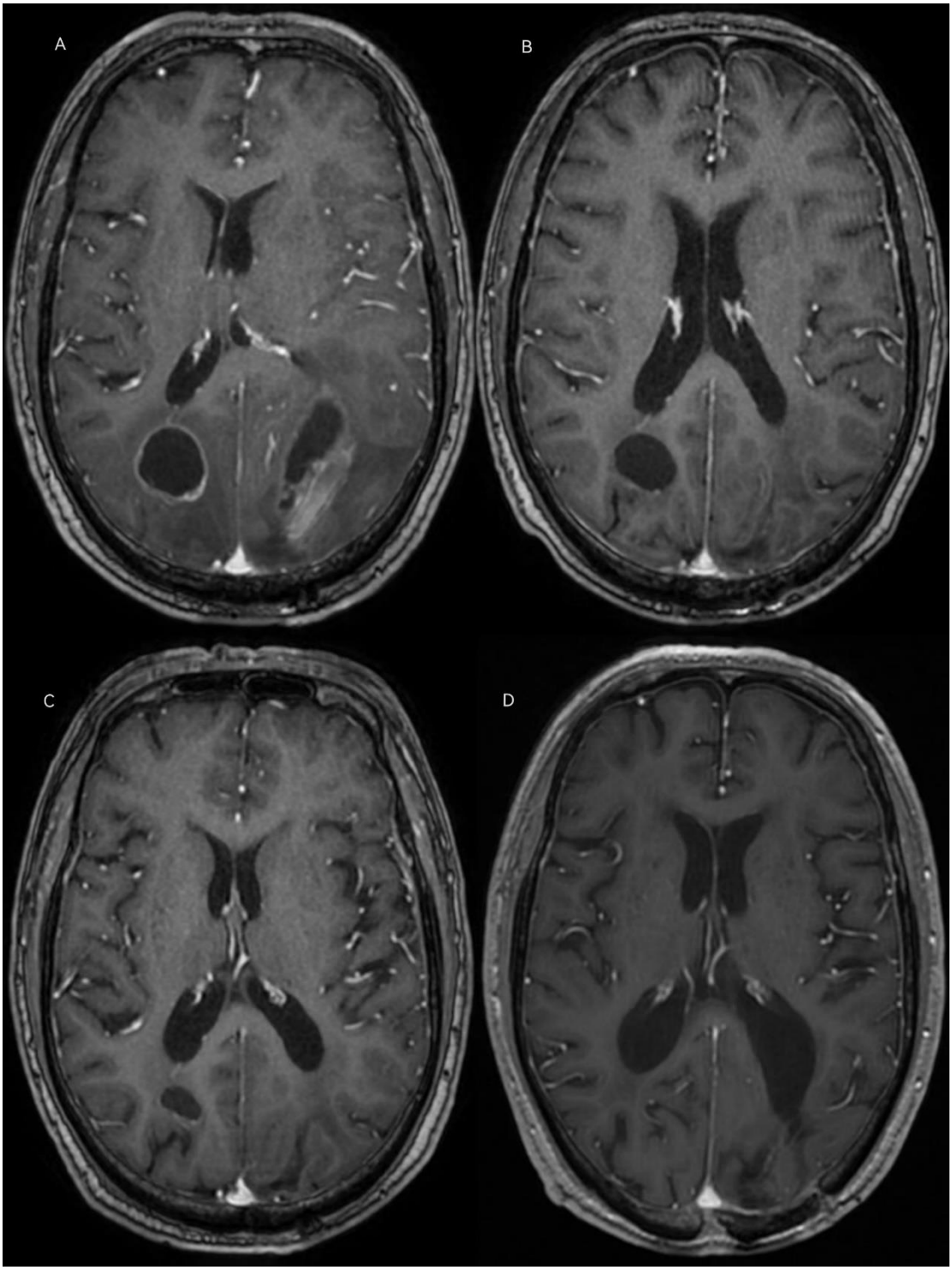

Figure 3. A-D Lesions of the right parietal lobe metastases before treatment (25mm×20mm×24mm), 1 month after treatment (21mm×14mm×18mm), and 3 months after treatment (12mm×9mm×11mm) and 2022-4-11CT (disappear)

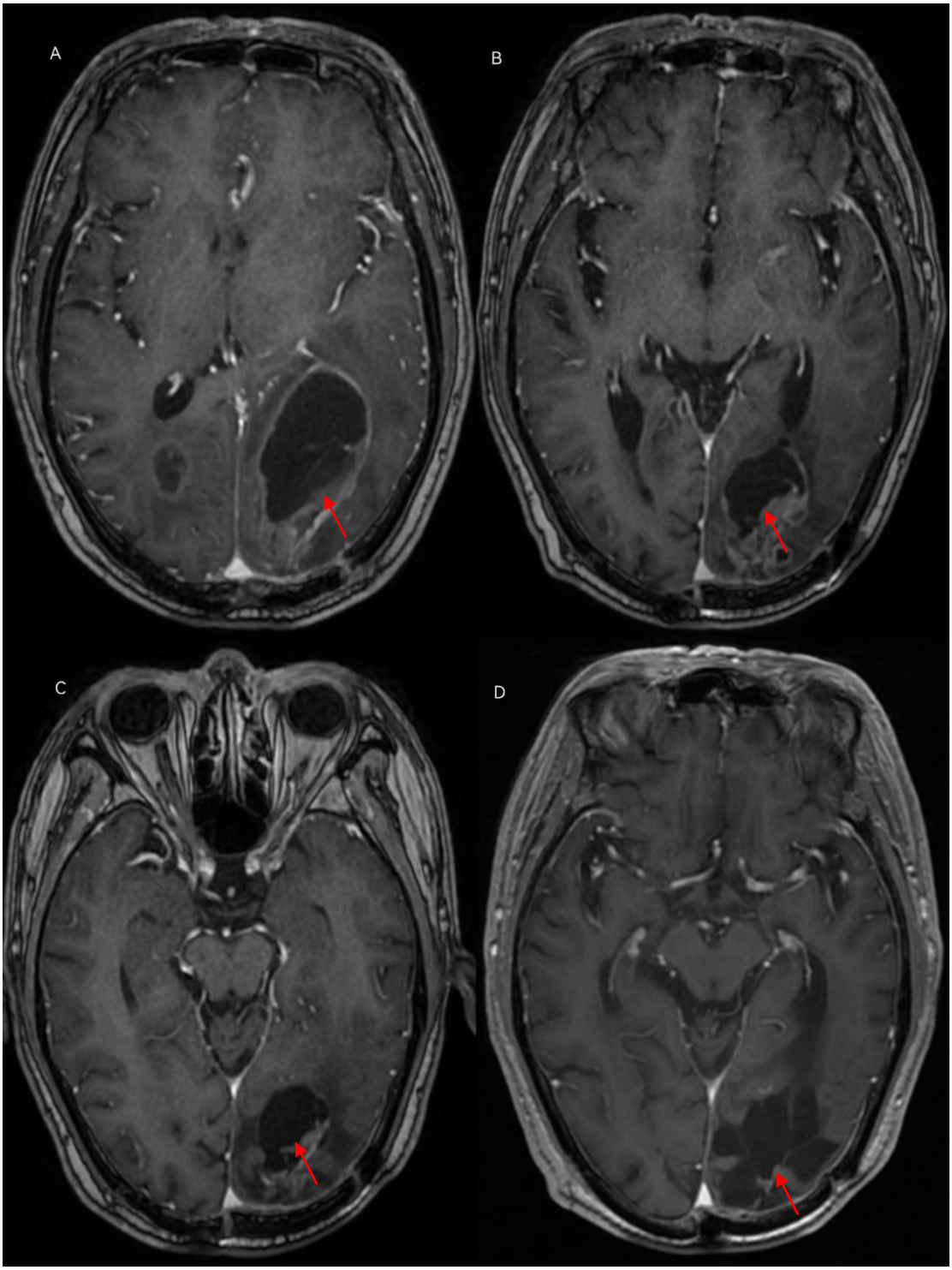

Figure 4. Lesions of left parietal occipital lobe metastases before treatment (70mm×42mm×60mm), 1 month after treatment (42mm×31mm×45mm), and 3 months after treatment (34mm×31mm×45mm) and 2022-4-11CT (29mm×20mm×16mm)

On 31-Jan-2020 the patient began to give 2 cycle EP (etoposide 150mg $D_{1\text{-}3}$, cisplatin 50mg $D_{1\text{-}2}$, 40mg D_3) chemotherapy. Review of abdomen and adrenal CT on 24 Mar 2020: left adrenal area occupancy (67mm × 56mm × 47 mm) (Fig.2-A). Cranial MRI: left parietal occipital lobe postoperative changes; The right parietal lobe (25 mm × 20mm × 24mm) (Fig.3-A), left parietal occipital lobe metastasis (70 mm × 42mm × 60 mm) (Fig.4-A), considering disease progression with a PS score of 3. Treatment with Toripalimab (PD-1 inhibitors) 240mg q3w was started on

27-Mar-2020 and whole brain radiotherapy DT: 30Gy/10F, 3Gy/F was performed from 01-Apr-2020 to 15-Apr-2020. Three cycles of immunotherapy were given after the end of radiotherapy, and the head MRI was reviewed on 18-Jun-2020: the right parietal lobe metastasis (12 × 9mm × 11 mm) (Fig.3-C), left parietal occipital lobe metastases (34 mm × 31mm × 45 mm) (Fig.4-C) were all decreased compared with the 2020-03-24 images. Radiotherapy for left adrenal focus performed from 06-Sep-2021 to 14-Oct-2021, 95.84% PTV: 60.03 Gy/29F. The efficacy was evaluated as PR. Abdominal CT on 15-Nov-2021: there was diminution of adrenal gland on the left side. Adrenal CT 12-Mar-2022: left adrenal area occupancy (33mm × 21mm × 18 mm) (Fig.2-D) significantly decreased compared to 2020-7-13(60 mm × 52mm × 47 mm) (Fig.2-C), and the efficacy was evaluated as maintaining PR. Cranial MRI in 11 April 2022: postoperative changes in left occipital region; The right parietal lobe metastasis disappeared (Fig.3-D) and the left parietal occipital lobe metastasis was 29 mm × 20mm × 16mm (Fig.4-D), smaller than before.

At present, the patient has been treated with 32 cycles of Toripalimab, during treatment tumor markers have decreased significantly, the primary and metastatic lesions have shrunk or disappeared. The treatment has been up to 4 years now, PS score 1, no rash and digestive tract, pneumonia and other immune adverse reactions have been observed. On 15 Mar 2021 review thyroid and neck lymph node color ultrasound: subacute thyroiditis. Upper hypoechogenic area of right thyroid lobe, cystic solid nodule of right thyroid lobe TI-RADs Category 3. Check the full items of thyroid function on 29 Apr 2021 suggest hypothyroidism, then give levothyroxine sodium symptomatic to patient, at present the patient has no obvious symptoms of hypothyroidism.

2. Discussion

SCLC is an aggressive cancer of neuroendocrine origin with a poor prognosis. SCLC patients have a short duration of symptoms, are prone to have metastatic disease (60-65%) (Ko, J., M.M. Winslow & J. Sage, 2021) and the most common sites of metastasis are contralateral lung, brain, liver, adrenal gland and bone. 80% of patients with SCLC develop brain metastases within 2 years of diagnosis (Wen, P., et al, 2020). PD-L1 inhibitor has been applied in the first-line treatment of extensive SCLC, but its prognosis remains poor and survival time is short, especially in patients with brain metastasis. Patients treated with PD-1 inhibitors which used in the third-line treatment only have short PFS benefit. In this case, the patient with brain and adrenal metastases SCLC with long-term survival and good quality of life is reported.

This study reports an elderly patient with SCLC who had brain and adrenal metastasis, for whom the conventional surgery, chemotherapy and radiotherapy were ineffective, but showed a partial response with the treatment with PD-1 inhibitor Toripalimab. At present, partial brain metastases disappeared, adrenal and partial brain metastases were significantly reduced, the PS score of the patient is 1 and the survival time has reached 4 years. PD-L1 inhibitor combined with chemotherapy is recommended by authoritative guidelines as the first-line standard treatment for extensive-stage SCLC (ES-SCLC). However, CASPIAN showed that the median overall survival of durvalumab combined chemotherapy and chemotherapy alone group was 14.4 months vs 10.9 months (Paz-Ares, L., et al, 2019), and the median overall survival was only improved by about 3 months. Nivolumab and pembrolizumab, as third-line drugs for ES-SCLC, only benefit from PFS. This patient benefited significantly from the use of the PD-1 inhibitor Toripalimab. Qu, Y., et al. reported a case of ES-SCLC patient treated with Toripalimab, who has survived for 17 months and only had grade 2 immune pneumonia (Qu, Y., et al, 2021).

There are surgical, chemotherapy, radiotherapy, targeted therapy and emerging immunotherapies for the treatment of SCLC brain metastases (Tsoukalas N, Aravantinou-Fatorou E, Baxevanos P, et al, 2018). Due to the existence of blood-brain barrier, the concentration of chemotherapeutic drugs in cerebrospinal fluid is very low, which has little effect on SCLC brain metastasis. Previous studies have shown that patients with small-cell lung cancer brain metastases treated with chemotherapy have a median progression free survival of 3 months and poor survival outcomes, with a median overall survival of approximately 10 months (Zhou, T., et al, 2020). This patient underwent surgery for brain metastases and 2 cycles of postoperative chemotherapy for intracranial lesion progression, after which she underwent radiotherapy. Radiotherapy can exert immunomodulatory

effects by increasing antigen release from tumour cells, upregulating MHC molecule expression on tumour cells, enhancing antigen-presenting cell phagocytosis, promoting antigen-presenting cell and T-cell differentiation, and modulating tumour immune checkpoint expression (Wang, Y., et al, 2019). The patient had an intracranial recurrence 2 months after radiotherapy, treated with Toripalimab, after which the nidus radiographically disappeared or lessened. Immune checkpoint inhibitors are able to enhance tumor specific T-cell responses, and activated T-cells are able to permeate through an intact blood-brain barrier (Reck, M., D. Heigener & N. Reinmuth, 2016). Duvalizumab combined with chemotherapy showed the same benefit trend as the general population in patients with brain metastasis at baseline and Caspian (Paz-Ares, L., et al, 2019) results showed that duvalizumab + EP could continuously improve OS and PFS in patients with brain metastasis. Keynote 028, a study of pembrolizumab treated in patients with ES-SCLC (including stable SCLC patients with brain metastases), reported a mORR of 33%, a DOR of 19.4 months, a mPFS of 1.9 months, and a mOS of 9.7 months in 24 patients, showing that pabolizumab has durable antitumour activity (Chung, H.C., et al, 2020). Immune agents have shown promising efficacy for the treatment of patients with SCLC brain metastases, but further validation in large trials is lacking.

A study reported that the incidence of grade 3 immune pneumonitis after the use of durvalumab was 14.3% (Jung, H.A., et al, 2020). This patient had only mild hypothyroidism after 12 months of treatment with Toripalimab, and after 25 months of follow-up efficacy was assessed as PR, quality of life was good, and no immune adverse effects such as rash, digestive tract and pneumonia were observed. The side effect that occurred after the use of Toripalimab was acceptable.

This is a successful case of a patient with metastatic small cell lung cancer who progressed on initial treatment with chemotherapy, recurred after radiotherapy, and finally have significant survival benefit and acceptable toxicity with single agent treatment of Toripalimab. This case can provide a hopeful treatment modality for patients with metastatic small cell lung cancer.

Acknowledgments

AXS. composed the manuscript and literature review; SY. and LYY. provided figures and pathology review; SY, XHH, SHL had the acquisition, analysis or interpretation of data for the work, revising it critically for important intellectual content, final approval of the version to be published; AXS made the decision to submit the article for publication.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Appendix

Informed Consent

The content of the conversation: Patient Hao Guimin, he was hospitalized in our hospital in January 2020, the diagnosis was: small cell lung cancer. After the implementation of chemotherapy and radiation therapy, patient was given 30 cycles of Toripalimab therapy for primary lesions, metastases and improve survival. At present, the follow-up is more than 2 years, the tumor is shrinking, there is no recurrence of metastasis, and the efficacy evaluation PR. In view of the low survival rate, few treatment methods and poor prognosis of patients with metastatic small cell lung cancer, its diagnosis and treatment process is collated and published for the reference of other medical workers.

Patient or surrogate opinion:

Signature of the patient or surrogate: Date:

Patient provided written informed consent.

Consent was obtained from the patient's relatives.

Statement

This is to certify that the author provided the patient with written informed consent for the publication of the case, and has signed it.

Signature of the author:

Signature of the patient or surrogate: Date: