Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Diagnostic Dilemma of Rapidly Progressive Neurological Symptoms in Extensive-Stage Small-Cell Lung Cancer Patients Treated with Immune Checkpoint Inhibitors: A Case Report and Literature Review

YULEI SHEN
Beijing University of Chinese Medicine
CHAO WANG
China-Japan Friendship Hospital
ZHENING LIU
Beijing University of Chinese Medicine
JIANGHUI DUAN
China-Japan Friendship Hospital
YUMIN ZHENG
Beijing University of Chinese Medicine
HUIJING DONG
Beijing University of Chinese Medicine
HUIJUAN CUI
cuihj1963@sina.com

China-Japan Friendship Hospital

Case Report

Keywords: Small Cell Lung Cancer, Leptomeningeal Metastasis, Immune Checkpoint Inhibitors, Neurological Symptoms, Differential Diagnosis

Posted Date: June 15th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9614450/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Small-cell lung cancer (SCLC) is an aggressive pulmonary tumor characterized by rapid progression and early dissemination. With advances in diagnostic techniques and therapeutic strategies, multimodal treatments, including chemotherapy, radiotherapy, and immunotherapy, have been widely adopted in clinical practice and have improved survival outcomes. However, neurological manifestations associated with SCLC often present with heterogeneous and atypical features, posing significant diagnostic challenges. In multimodal treatment, accurate recognition and differential diagnosis of neurological signs are crucial to its effectiveness. This study reports a patient initially diagnosed with extensive-stage SCLC who achieved a partial response (PR) on imaging after combined radiotherapy, chemotherapy, and immunotherapy. Despite this favorable initial response, the patient experienced a rapid progression of neurological symptoms. Further investigation with contrast-enhanced magnetic resonance imaging (MRI) and cerebrospinal fluid analysis confirmed rare, extensive metastatic involvement of the medulla oblongata, brainstem, and the entire spinal meninges. By analyzing the treatment course and diagnostic process, this study provides a clinical reference for evaluating and differentiating neurological symptoms in patients with SCLC.

Introduction

Small-cell lung cancer (SCLC) is a highly aggressive subtype of lung tumors characterized by rapid disease progression, strong invasiveness, and poor overall prognosis. It accounts for approximately 10–15% of lung cancer cases worldwide, with a 5-year survival rate of < 5% in patients with extensive-stage disease [1]. Recently, advances in diagnostic modalities, including computed tomography (CT), positron emission tomography–computed tomography (PET-CT), and liquid biopsy, together with continuous refinement of therapeutic strategies, have substantially improved the clinical management of SCLC. The implementation of multimodal treatment approaches, such as combination chemotherapy, thoracic radiotherapy, whole-brain radiotherapy (WBRT), and immune checkpoint inhibitors (ICIs), has led to significant survival benefits across different stages of treatment [2,3]. However, the prognosis for patients with extensive-stage SCLC remains poor, largely due to the high incidence of distant metastases, particularly those involving the central nervous system (CNS), which continue to present major therapeutic challenges [4,5].

Neurological and neurocognitive manifestations associated with SCLC showed significant clinical heterogeneity, making accurate diagnosis particularly challenging. The underlying etiologies are multifactorial and include direct tumor invasion, resulting in brain parenchymal metastases and leptomeningeal metastases (LM), as well as treatment-related toxicities such as radiation-induced brain injury (RIBI) and immune-related adverse events (irAEs). Moreover, paraneoplastic neurological syndromes (PNS) are another important cause of neurological dysfunction in this patient population [6]. In the case of more diverse treatments, overlapping clinical presentations arising from different pathogenic mechanisms further complicate differential diagnosis. The National Comprehensive Cancer Network (NCCN) guidelines state that accurate etiological differentiation of neurological symptoms is a crucial

prerequisite for appropriate clinical decision-making, as distinct causes may necessitate significantly different therapeutic strategies [7]. Therefore, timely recognition and precise identification of neurocognitive symptoms in patients with SCLC are essential for optimizing treatment outcomes and improving prognosis.

This study presents a patient initially diagnosed with extensive-stage SCLC who achieved a PR on imaging after combined radiotherapy, chemotherapy, and immunotherapy. Despite this initial response, the patient developed rapidly progressive neurological symptoms. Further diagnostic analyses, including contrast-enhanced magnetic resonance imaging (MRI) and cerebrospinal fluid cytology, confirmed rare, extensive metastatic involvement of the medulla oblongata and brainstem meninges, with diffuse metastasis throughout the spinal meninges. Through a systematic analysis of the treatment course, clinical manifestations, and differential diagnostic considerations across multiple potential etiologies, this case provides a reliable reference and insight for clinicians managing SCLC patients presenting with complex neurological symptoms.

Case report

A 52-year-old man presented in October 2023 with progressive exertional dyspnea in the China-Japan Friendship Hospital (Beijing, China). The patient was previously healthy, with no definite family history of malignant tumors or neurological diseases. He had a smoking history of more than 20 years. Chest CT showed a mass in the mediastinum along with a lesion in the left hilar region. PET/CT revealed a hypermetabolic lesion adjacent to the left hilum, associated with multiple areas of bronchial narrowing and interruption (Fig. 1A). Increased metabolic activity was also observed in lymph nodes within the mediastinum, left hilum, and retroperitoneal regions. Contrast-enhanced MRI of the brain identified a metastatic lesion in the right occipital lobe (Fig. 2A). In November 2023, EBUS-TBNA of the left hilar lesion confirmed small cell carcinoma. Immunohistochemical analysis showed positivity for synaptophysin (Syn) and thyroid transcription factor-1 (TTF-1), with a Ki-67 (MIB-1) proliferation index of approximately 90%. Based on these findings, a diagnosis of extensive-stage SCLC originating from the left lung was established.

Systemic therapy was initiated in December 2023 with an EC chemotherapy regimen, administered for four cycles (1–4). Imaging reassessment in February 2024 showed a reduction in thoracic tumor burden (Fig. 1B). The same contrast-enhanced brain MRI revealed regression of the right occipital metastasis, corresponding to a PR (Fig. 2B). Between March and April 2024, two additional cycles (cycles 5–6) of EC chemotherapy were administered. PET/CT imaging showed complete recovery of the previously hypermetabolic left hilar mass (Fig. 1C), along with a significant decrease in both size and metabolic activity of lymph nodes in the mediastinal, hilar, and retroperitoneal regions, consistent with sustained PR (Fig. 1E). After the seventh cycle of chemotherapy in May 2024, consolidative thoracic radiotherapy was delivered over ten fractions to enhance local disease control. Contrast-enhanced brain MRI in May 2024 demonstrated nodular hyperintense lesions in the subcortical regions of the bilateral parietal lobes (Fig. 2C1), left frontal lobe (Fig. 2C2), and left insular cortex (Fig. 2C3).

The eighth cycle of EC chemotherapy was completed in June 2024. Follow-up chest CT in July 2024 showed stable pulmonary disease (Fig. 1D); however, contrast-enhanced brain MRI revealed Nodular hyperintense lesions in the subcortical regions of the bilateral parietal lobes (Fig. 2D1), left frontal lobe (Fig. 2D2), and left insular cortex (Fig. 2D3) were increased in size compared with prior imaging. New hyperintense nodules were seen in the bilateral occipital lobes (Fig. 2D4), which were not present 2 months earlier (Fig. 2C4). Accordingly, from July to August 2024, whole-brain radiotherapy (PTV 3000 cGy in 10 fractions) was administered, along with focal boost radiotherapy to intracranial lesions (95% PGTV, 14 Gy delivered in 7 fractions of 2.0 Gy). During this period, cycles 9 and 10 of EC chemotherapy were completed. Next, maintenance therapy consisting of alternating oral chemotherapy combined with serplulimab and temozolomide/etoposide capsules was initiated and continued for five cycles until February 2025.

In December 2024, the patient developed new-onset neurological symptoms, including persistent hiccups, bilateral hand tremors, impaired balance with a positive Romberg sign, gait deviation, and urinary retention. Neurological deterioration progressed rapidly, manifesting as episodic memory impairment, cognitive dysfunction, somnolence, followed by muscle weakness, aphasia, and loss of bladder and bowel control. Comprehensive serum cytokine profiling revealed no significant abnormalities. Contrast-enhanced brain MRI showed irregular linear enhancement involving the medulla oblongata and brainstem meninges, while contrast-enhanced lumbar spine MRI showed diffuse meningeal enhancement (Fig. 3). Lumbar puncture was performed, and CSF analysis revealed higher protein concentration, reduced chloride levels, and increased glucose. Autoantibody testing for neuronal surface and intracellular antigens (NMDA, GAD, VGKC, Ri, Hu, and Yo) yielded negative results. Further CSF analysis (cryptococcal antigen testing, metagenomic sequencing, and acid-fast bacilli staining) was unremarkable. Cytological examination of the CSF identified malignant small cell carcinoma cells, confirming the diagnosis of leptomeningeal and spinal meningeal metastases. Last, an Ommaya reservoir was implanted in the left lateral ventricle. The patient received intrathecal selinexor at 10 mg every 10 days for a total of five administrations, in combination with two cycles of systemic chemotherapy consisting of temozolomide (240 mg on days 1–5) and cisplatin (40 mg on days 1–2), repeated every 21 days. The patient demonstrated good adherence to the treatment regimen throughout the hospitalization, and no significant intolerance or adverse reactions were observed. Unfortunately, this patient eventually passed away three months later.

Discussion

The patient was diagnosed with SCLC complicated by brain metastasis. After receiving chemotherapy, radiotherapy, and immunotherapy, a significant reduction in the primary pulmonary lesions was observed; however, new neurological symptoms developed later. Neuroimaging findings raised suspicion for intracranial metastatic progression and possible meningeal involvement, necessitating further examination of the underlying cause. Accordingly, the differential diagnosis primarily focuses on identifying the etiology of the neurological manifestations and imaging abnormalities, with particular consideration given to tumour progression, treatment-related effects, infectious processes, and

autoimmune mechanisms, all of which are critical for guiding individualized therapeutic decision-making. Patients with malignant tumors are at increased risk of infectious meningitis due to impaired immune function [8,9]. The clinical presentation of infectious meningitis is heterogeneous. Acute forms typically present with fever, worsening headache, and positive meningeal signs, whereas chronic bacterial or fungal meningitis may lack fever or classical meningeal irritation signs, increasing the risk of early misdiagnosis [10]. Therefore, laboratory examinations and imaging studies are essential for accurate differentiation, and prompt initiation of empirical anti-infective therapy is recommended when clinically indicated [11]. In this case, a lumbar puncture was performed, and negative CSF microbiological results effectively excluded infectious meningitis.

A retrospective analysis of the TriNetX oncology database found that approximately 35% of patients with newly diagnosed SCLC present with brain metastases, including parenchymal and leptomeningeal metastases (LM). Among neurological complications associated with SCLC, leptomeningeal carcinomatosis accounts for only 6.7% of cases [12]. The reported median interval between the initial diagnosis of metastasis and confirmation of LM is 0.5 years, with a wide range extending up to 14.9 years [13]. LM is characterized by diffuse, multifocal, or focal infiltration of malignant cells within the brain parenchyma, subarachnoid space, and other CSF compartments, leading to disruption of neural pathways and a broad spectrum of neurological symptoms [14]. Given that CSF circulates throughout the central nervous system, LM often presents with discontinuous lesions, and clinical manifestations vary depending on the neuroanatomical regions involved. In addition to intracranial symptoms, spinal cord-related signs may also be observed [15]. Although histopathological confirmation remains the diagnostic gold standard, invasive brain tissue sampling is often impractical. Therefore, diagnosis typically relies on CSF cytology in combination with contrast-enhanced MRI. Despite a favourable therapeutic response of the primary lung lesion in this patient, the rapid onset and progression of neurological symptoms were discordant with systemic disease control. Contrast-enhanced MRI of the brain and thoracic spine revealed irregular meningeal enhancement involving the medulla oblongata and the entire spinal meninges, raising a strong suspicion for leptomeningeal metastasis. Given the patient's and family's preference for aggressive management, repeated lumbar punctures were performed. While initial CSF examinations were negative for malignant cells, atypical cells consistent with small-cell carcinoma were eventually identified in a CSF centrifugation smear in March 2025, confirming the diagnosis of CSF metastasis.

Leptomeningeal metastasis is associated with an extremely poor prognosis. Tumour-derived complement component C3 has been shown to disrupt the blood-brain barrier (BBB) by interacting with the C3a receptor, thus facilitating tumor cell invasion into the leptomeningeal compartment [16–19]. Current therapeutic strategies are largely palliative. Although intrathecal chemotherapy may be considered in selected patients [20], clinical outcomes remain unfavorable, with reported median overall survival ranging from 1.9 to 3.0 months [13,21].

The patient was initially suspected of harboring a metastatic lesion in the right occipital lobe. After systemic chemotherapy and thoracic radiotherapy, a favourable therapeutic response was achieved, with both the primary pulmonary lesion and intracranial metastatic foci meeting the criteria for PR. However, seven months after treatment completion, newly emerged metastatic nodules were detected in both occipital lobes, raising concern for localized intracranial disease progression. According to the NCCN Clinical Practice Guidelines for SCLC, whole-brain radiotherapy (WBRT) combined with stereotactic radiosurgery (SRS) is recommended for the management of brain metastases in SCLC patients [22]. Evidence from a multicentre clinical study demonstrated that combined WBRT and focal radiotherapy significantly prolonged intracranial progression-free survival (iPFS) compared with WBRT alone (10.8 vs. 6.5 months, $p = 0.005$) and SRS alone (10.8 vs. 7.5 months, $p = 0.032$), indicating a clear therapeutic advantage [23]. Based on these findings, WBRT with a focal boost was administered to control the progressive intracranial lesions. Considering the risk of neurocognitive impairment associated with WBRT, particularly involving memory and language dysfunction [24], radiation-induced brain injury (RIBI) was initially considered when intermittent amnesia and cognitive decline developed. However, the rapid evolution of additional neurological deficits, including muscle weakness, aphasia, and delirium, was inconsistent with the typical clinical course of RIBI. Moreover, contrast-enhanced MRI of the brain and thoracic spine revealed linear meningeal enhancement involving the medulla oblongata and brainstem, without the hallmark radiographic features of RIBI, such as cerebral parenchymal necrosis or ventricular system injury [25]. These findings suggested that while WBRT may have contributed to cognitive impairment, it was unlikely to be the primary cause of the observed neurological deterioration. Paraneoplastic neurological syndromes (PNS) are immune-mediated disorders triggered by tumor-associated antigens and arise from cross-reactive immune responses directed against both neoplastic tissue and the nervous system [26,27]. SCLC is the malignancy most frequently associated with PNS, accounting for approximately 3–5% of all cases [28]. In SCLC-related PNS, neurological symptoms often precede tumor diagnosis [29,30]. Diagnosis primarily relies on identifying tumor-associated autoantibodies, including anti-GABABR, anti-Hu, and anti-SOX1 antibodies, which predominantly target intracellular neuronal antigens [31]. A nine-year epidemiological study reported an increasing incidence of PNS, with anti-Yo (30%) and anti-Hu (26%) antibodies representing the most common pathogenic subtypes. Limbic encephalitis was the most frequent phenotype (31%), followed by paraneoplastic cerebellar degeneration (28%) [32]. Other neurological manifestations include myasthenia gravis, Lambert–Eaton myasthenic syndrome, and limbic encephalitis [33].

In clinical practice, examination of suspected PNS requires integrating neurological symptom patterns with the characteristic features of specific PNS subtypes, supported by comprehensive autoantibody screening. In the present case, all relevant paraneoplastic antibody tests were negative, effectively excluding a diagnosis of PNS. At the molecular level, SCLC-associated PNS shows distinct characteristics. Patients with anti-GABABR antibodies commonly present with seizures, cognitive impairment, and psychiatric symptoms [34], whereas anti-Hu–associated PNS is predominantly mediated by cytotoxic T-cell immune responses [35,36]. The potassium channel tetramerization domain-containing

protein 16 (KCTD16) has been proposed as a molecular marker distinguishing anti-GABABR–positive from anti-Hu–positive SCLC cases [37]. In comparison, anti-SOX1-positive patients typically lack characteristic imaging findings, and there is no consensus on optimal treatment or on the assessment of efficacy for this subtype [38]. Elevated SOX2 protein expression may play a critical role in inducing anti-SOX2-specific immune responses, potentially enhancing immune surveillance and tumor immune editing [39]. PNS-associated antibody titers correlate positively with tumor burden. Reductions in antibody levels following immunotherapy combined with chemotherapy have been associated with improved survival outcomes [40,41]. Therefore, assessment of tumor activity, including serum tumor markers such as neuron-specific enolase (NSE) and pro-gastrin-releasing peptide (ProGRP), as well as systemic imaging modalities such as chest CT and PET-CT, remains essential. Even in the context of stable systemic disease, progressive neurological symptoms should prompt continued consideration of PNS. Corticosteroids are first-line therapy due to their ability to rapidly suppress immune-mediated neuroinflammation. Intravenous immunoglobulin may be used in patients with steroid intolerance or an inadequate response, although therapeutic efficacy varies among PNS subtypes. Immunomodulatory therapies yield poorer outcomes in PNS associated with antibodies targeting intracellular antigens, whereas syndromes involving cell-surface neuronal antigens tend to respond more favorably [42].

SCLC is a highly aggressive neuroendocrine malignancy characterized by significant co-expression of tumor-associated and neural antigens [43–45]. This aberrant antigenic overlap enables ectopic expression of molecules that share high homology with normal neural-tissue antigens, thus disrupting immune homeostasis. Thus, SCLC not only has a strong predisposition for inducing or exacerbating PNS but also shows a substantially increased risk of irAEs in patients treated with immunotherapy. With the advent of immune checkpoint inhibitors (ICIs), survival outcomes for patients with advanced malignancies have significantly improved. However, the rising incidence and complexity of irAEs have emerged as major clinical challenges in achieving optimal therapeutic benefit [46,47]. Among these toxicities, neurological immune-related adverse events (N-irAEs), although relatively uncommon, show considerable clinical heterogeneity. They may involve any region of the central or peripheral nervous system and commonly present as immune-mediated encephalitis, meningitis, or myositis [48,49]. Moreover, by disrupting tumor immune tolerance and boosting systemic immune activation, immunotherapy not only enhances antitumor efficacy but may also enhance autoimmune phenomena, thus increasing both the incidence and severity of PNS. ICIs potentiate T-cell activation and clonal expansion, which can directly precipitate T-cell–mediated PNS. Similarly, ICIs promote antibody-mediated PNS through $CD4^+$ helper T-cell-driven activation of memory B cells and antibody-secreting plasma cells [50,51]. Clinical evidence indicates that patients with circulating autoantibodies before treatment initiation face a significantly elevated risk of developing ICI-related irAEs. These findings suggest that ICIs do not induce de novo autoantibody production but rather boost pre-existing autoimmune responses, ultimately triggering PNS in susceptible individuals [52–55]. This immunological background provides a possible explanation for the higher susceptibility of SCLC patients to immune-mediated toxicities and the frequent occurrence or exacerbation of PNS during ICI therapy. In addition to adaptive immune mechanisms, ICIs may directly

promote neuroinflammation by activating the complement cascade [56–58]and promoting the infiltration of $CD4^+$ T cells into the central nervous system. Upon encountering homologous antigens within neural tissue, these reactivated T cells can sustain the release of pro-inflammatory cytokines, including IL-17, initiating a self-perpetuating neuroinflammatory cascade that culminates in irreversible neuronal injury [59]. Accurate differentiation of ICI-related N-irAEs from other neurological complications has become increasingly critical in contemporary oncology practice. Comprehensive analysis should integrate neurological symptom profiles with serological and cerebrospinal fluid analyses, as well as advanced neuroimaging findings. Therapeutic management should prioritize prompt discontinuation of ICIs and early initiation of immunosuppressive treatment, typically with high-dose corticosteroids and intravenous immunoglobulin [7].

Looking forward, therapeutic strategies for PNS in the era of immunotherapy are transitioning from nonspecific immunosuppression toward precision-based and integrative approaches that aim to preserve the antitumor benefits of ICIs while selectively reducing neurological injury [60]. Although the management of ICI-induced PNS largely parallels that of non–ICI-associated PNS, patients harboring specific autoantibodies, such as anti-NMDA receptor, anti–aquaporin-4 (AQP4), and anti-GABA receptor antibodies, appear to be at significantly increased risk of severe central nervous system autoimmunity following ICI exposure [61,62]. These antibodies may therefore serve as early-warning biomarkers of PNS development. In addition to autoantibody surveillance, emerging evidence suggests that dynamic monitoring of inflammatory cytokines, including IL-6 and IL-17, and profiling of the gut microbiota may provide additional predictive value for assessing susceptibility to N-irAEs [63]. These advances hold promise for establishing a precise diagnostic and therapeutic platform for ICI-related neurotoxicity, promoting safer and more effective integration of immunotherapy into clinical practice.

Conclusion

The increasing combination of ICIs into the treatment paradigm for SCLC has significantly complicated the diagnostic evaluation of neurological symptoms. The higher susceptibility of SCLC patients to neurological immune-related adverse events, together with the high incidence of brain and leptomeningeal metastases, results in substantial overlap in clinical and imaging manifestations. These factors highlight the critical importance of a systematic, multidisciplinary diagnostic approach to accurately distinguish treatment-related neurotoxicity from tumor-associated neurological progression, thereby enabling timely and appropriate clinical management.

Declarations

Ethical Approval

The study was approved by the Ethics Committee of China-Japan Hospital(2023-KY-134), in accordance with the Declaration of Helsinki.

Consent to participate

Informed consent to participate was obtained from the patient's legal guardians.

Consent to publish

Informed consent to publish this case report and any accompanying images was obtained from the patient.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This work was supported by National High Level Hospital Clinical Research Funding (2025-NHLHCRF-JBGS-A-WZ-16) and China-Japan Friendship Hospital.

Author Contribution

YS and CW wrote the original draft of the manuscript; these authors contributed equally to this work. ZL reviewed and edited it. JD was responsible for image acquisition and analysis, YZ for conceptualization, and HD confirmed the authenticity of all the raw data, and HC supervised the study. All authors read and approved the final version of the manuscript.

Acknowledgements

Not applicable.

Data Availability

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Patient Perspective

The patient’s family stated that they fully understood the rapid progression and complexity of the neurological symptoms. They expressed satisfaction with the timely diagnostic process and the clinical

improvement observed after the treatment strategy was adjusted.

References

1. Small cell lung cancer. Global clinical trial landscape (2025) | Novotech CRO. https://novotech-cro.com/reports/small-cell-lung-cancer-global-clinical-trial-landscape-2025
2. Cao Z, Deng K, Jiang J, Tian K, Wang B. Combined treatment of small cell lung cancer using radiotherapy and immunotherapy: Challenges and updates. Biomed Pharmacother. 2025;182:117727.
3. Li J, et al. Neoadjuvant low-dose radiotherapy plus durvalumab and chemotherapy for potentially resectable stage III NSCLC: A phase ib dose-escalation study. Radiother Oncol. 2024;196:110316.
4. Sankar K, et al. Real-world treatment patterns and clinical outcomes in patients with extensive-stage small cell lung cancer treated with first-line platinum-based chemotherapy and ≥ 2 subsequent lines of therapy in the united states. Adv Ther. 2025. https://doi.org/10.1007/s12325-025-03408-z.
5. Accurate treatment of small cell lung cancer. Current progress, new challenges and expectations. Biochim et Biophys Acta (BBA) - Reviews Cancer. 2022;1877:188798.
6. Kim SY, Park HS, Chiang AC. Small cell lung cancer: A review. JAMA. 2025;333:1906–17.
7. Guidelines detail. *NCCN* https://www.nccn.org/guidelines/guidelines-detailcategory=3&id=1486
8. WHO guidelines on meningitis diagnosis. treatment and care. https://www.who.int/publications/i/item/9789240108042
9. Pomar V, et al. Characteristics and outcome of spontaneous bacterial meningitis in patients with cancer compared to patients without cancer. Med (Baltim). 2017;96:e6899.
10. Geiseler PJ, Nelson KE. Bacterial meningitis without clinical signs of meningeal irritation. South Med J. 1982;75:448–50.
11. McCabe WR. Empiric therapy for bacterial meningitis. Rev Infect Dis. 1983;5(Suppl 1):S74–83.
12. Parker M, et al. Prevalence, treatment patterns, and survival of patients with brain metastases from small cell lung cancer: A retrospective study using the TriNetX oncology database. Neurooncol Pract. 2024;12:257–70.
13. Rinehardt H, et al. Assessment of leptomeningeal carcinomatosis diagnosis, management and outcomes in patients with solid tumors over a decade of experience. Eur J Breast Health. 2021;17:371–7.
14. Gleissner B, Chamberlain MC. Neoplastic meningitis. Lancet Neurol. 2006;5:443–52.
15. Leptomeningeal metastasis from. solid tumors. J Neurol Sci. 2020;411:116706.
16. Breaching barriers |. nature reviews cancer. https://www.nature.com/articles/nrc.2017.27
17. Zhao J, et al. Dura immunity configures leptomeningeal metastasis immunosuppression for cerebrospinal fluid barrier invasion. Nat Cancer. 2024;5:1940–61.

18. Rittberg R, Banerji S, Kim JO, Rathod S, Dawe DE. Treatment and prevention of brain metastases in small cell lung cancer. Am J Clin Oncol. 2021;44:629–38.
19. Mo F, Pellerino A, Soffietti R, Rudà R. Blood–brain barrier in brain tumors: Biology and clinical relevance. Int J Mol Sci. 2021;22:12654.
20. Montes deO, Delgado M, et al. The comparative treatment of intraventricular chemotherapy by ommaya reservoir vs. Lumbar puncture in patients with leptomeningeal carcinomatosis. Front Oncol. 2018;8:509.
21. Palmisciano P, et al. Leptomeningeal metastases of the spine: A systematic review. Anticancer Res. 2022;42:619–28.
22. Guidelines detail. *NCCN* https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1462
23. Ni M, et al. Whole brain radiation therapy plus focal boost may be a suitable strategy for brain metastases in SCLC patients: A multi-center study. Radiat Oncol. 2020;15:70.
24. Gui C, et al. A prospective evaluation of whole brain volume loss and neurocognitive decline following hippocampal-sparing prophylactic cranial irradiation for limited-stage small-cell lung cancer. J Neurooncol. 2019;144:351–8.
25. Witzmann K, Raschke F, Troost EG. C. MR image changes of normal-appearing brain tissue after radiotherapy. Cancers (Basel). 2021;13:1573.
26. Dalmau J, Graus F. Antibody-mediated encephalitis. N Engl J Med. 2018;378:840–51.
27. Updated diagnostic criteria. for paraneoplastic neurologic syndromes | neurology neuroimmunology & neuroinflammation. https://www.neurology.org/doi/10.1212/NXI.0000000000001014
28. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. Lancet Neurol. 2008;7:327–40.
29. Dalmau J, et al. Major histocompatibility proteins, anti-hu antibodies, and paraneoplastic encephalomyelitis in neuroblastoma and small cell lung cancer. Cancer. 1995;75:99–109.
30. Zhang Y, Yang D, Weng L, Wang L. Early lung cancer diagnosis by biosensors. Int J Mol Sci. 2013;14:15479–509.
31. Devine MF, Kothapalli N, Elkhooly M, Dubey D. Paraneoplastic neurological syndromes: Clinical presentations and management. Ther Adv Neurol Disord. 2021;14:1756286420985323.
32. Vogrig A, et al. Epidemiology of paraneoplastic neurological syndromes: A population-based study. J Neurol. 2020;267:26–35.
33. Barahman M, Shamsaei G, Kashipazha D, Bahadoram M, Akade E. Paraneoplastic neurological syndromes of small cell lung cancer. Postep Psychiatr Neurol. 2024;33:80–92.
34. Jiang C, et al. SCLC and anti-GABABR encephalitis: A retrospective analysis of 60 cases in China. Thorac Cancer. 2022;13:804–10.
35. de Beukelaar JW, et al. Imbalances in circulating lymphocyte subsets in hu antibody associated paraneoplastic neurological syndromes. Eur J Neurol. 2007;14:1383–91.
36. Kazarian M, et al. Immune response in lung cancer mouse model mimics human anti-hu reactivity. J Neuroimmunol. 2009;217:38–45.

37. Vogrig A, et al. Different genetic signatures of small-cell lung cancer characterize anti-GABAB R and anti-hu paraneoplastic neurological syndromes. Ann Neurol. 2023;94:1102–15.
38. Sun X, et al. Anti-SOX1 antibodies in paraneoplastic neurological syndrome. J Clin Neurol. 2020;16:530–46.
39. Atakan S, et al. Autologous anti-SOX2 antibody responses reflect intensity but not frequency of antigen expression in small cell lung cancer. BMC Clin Pathol. 2014;14:24.
40. Hardy-Werbin M, et al. Assessment of neuronal autoantibodies in patients with small cell lung cancer treated with chemotherapy with or without ipilimumab. Oncoimmunology. 2017;7:e1395125.
41. Winter SF, et al. Antibodies against autologous tumor cell proteins in patients with small-cell lung cancer: Association with improved survival. J Natl Cancer Inst. 1993;85:2012–8.
42. Honnorat J. Early-onset immunotherapy by intravenous immunoglobulin and corticosteroids in well characterized onconeural-antibody-positive paraneoplastic neurological syndrome. Clin Exp Immunol. 2014;178:127–9.
43. Güre AO, et al. Serological identification of embryonic neural proteins as highly immunogenic tumor antigens in small cell lung cancer. Proc Natl Acad Sci U S A. 2000;97:4198–203.
44. Torà M, Graus F, de Bolòs C, Real FX. Cell surface expression of paraneoplastic encephalomyelitis/sensory neuronopathy-associated hu antigens in small-cell lung cancers and neuroblastomas. Neurology. 1997;48:735–41.
45. Ichimura M, et al. Tissue distribution of pathological lesions and hu antigen expression in paraneoplastic sensory neuronopathy. Acta Neuropathol. 1998;95:641–8.
46. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378:158–68.
47. Farina A, et al. Neurological adverse events of immune checkpoint inhibitors and the development of paraneoplastic neurological syndromes. Lancet Neurol. 2024;23:81–94.
48. Haugh AM, Probasco JC, Johnson DB. Neurologic complications of immune checkpoint inhibitors. Expert Opin Drug Saf. 2020;19:479–88.
49. Cuzzubbo S, Carpentier AF. Neurological adverse events of immune checkpoint blockade: From pathophysiology to treatment. Curr Opin Neurol. 2022;35:814.
50. Duong SL, Prüss H. Paraneoplastic autoimmune neurological syndromes and the role of immune checkpoint inhibitors. Neurotherapeutics. 2022;19:848–63.
51. Kanie K, et al. Mechanistic insights into immune checkpoint inhibitor-related hypophysitis: A form of paraneoplastic syndrome. Cancer Immunol Immunother. 2021;70:3669–77.
52. Zhang L, Fan S, Wang J, Ren H, Guan H. Antibody-positive paraneoplastic neurological syndromes associated with immune checkpoint inhibitors: A systematic review. J Neurol. 2025;272:249.
53. Urrego-Callejas T, et al. A manifestation of immune related adverse events of cancer immunotherapy. Revista Colombiana de Reumatología (English Edition). 2022;29:3–8. Autoantibodies.

54. Aoun R, Gratch D, Kaminetzky D, Kister I. Immune checkpoint inhibitors in patients with pre-existing neurologic autoimmune disorders. Curr Neurol Neurosci Rep. 2023;23:735–50.
55. Gill A, et al. A case series of PD-1 inhibitor-associated paraneoplastic neurologic syndromes. J Neuroimmunol. 2019;334:576980.
56. Chauhan P, Lokensgard JR. Glial cell expression of PD-L1. Int J Mol Sci. 2019;20:1677.
57. Manenti S, et al. PD-1/PD-L axis in neuroinflammation: New insights. Front Neurol. 2022;13:877936.
58. Herold M, et al. B7-H1 selectively controls TH17 differentiation and central nervous system autoimmunity via a novel non-PD-1-mediated pathway. J Immunol. 2015;195:3584–95.
59. Dimitriou F, et al. A targetable type III immune response with increase of IL-17A expressing CD4 + T cells is associated with immunotherapy-induced toxicity in melanoma. Nat Cancer. 2024;5:1390–408.
60. Jean MJ, Samkoff L, Mohile N. Management of paraneoplastic syndromes in the era of immune checkpoint inhibitors. Curr Treat Options Oncol. 2024;25:42–65.
61. Sechi E, et al. Neurologic autoimmunity and immune checkpoint inhibitors. Neurology. 2020;95:e2442–52.
62. Immune checkpoint inhibitor-. associated central nervous system autoimmunity - valencia-sanchez – 2023 - european journal of neurology - wiley online library. https://onlinelibrary.wiley.com/doi/10.1111/ene.15835
63. Vogrig A, et al. Prediction, prevention, and precision treatment of immune checkpoint inhibitor neurological toxicity using autoantibodies, cytokines, and microbiota. Front Immunol. 2025;16:1548897.

Figures

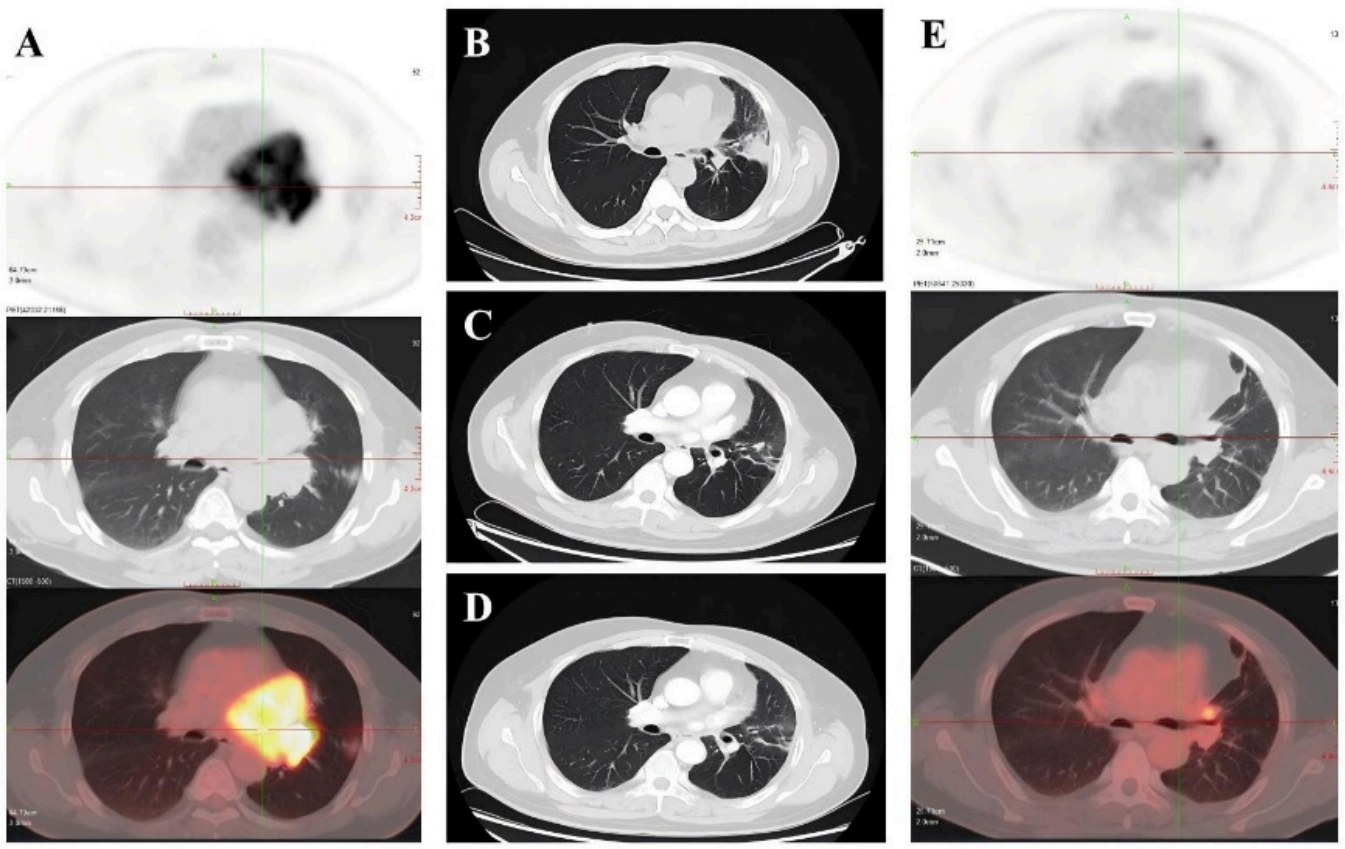


Figure 1

Longitudinal evolution of pulmonary lesions and metabolic response to treatment.(A) Initial PET/CT scan (November 2023) demonstrates an irregular parahilar mass in the left lung (7.1×6.8 cm) with heterogeneously increased FDG uptake (SUVmax:11.3). The lesion encases the left pulmonary artery and results in multiple stenoses and occlusions of the left main and upper lobe bronchi. **(B)** Follow-up chest CT (February 2024) reveals a reduction in left lung volume accompanied by persistent left hilar enlargement. **(C)** Chest CT (May 2024) shows a decrease in the size of the primary left lung mass. Multiple patchy opacities and cavitary lesions with mild enhancement are noted in the left upper lobe; compared with the previous scan, the cavities have enlarged with thinning walls, while the patchy opacities have regressed. **(D)** Chest CT (July 2024) shows stable patchy opacities and cavitary lesions in the left upper lobe with no significant interval change. **(E)** PET/CT (May 2024) shows persistent patchy and cavitary lesions in the left upper lobe with localized hypermetabolism (SUVmax:4.0). Notably, the previously observed hypermetabolic parahilar mass has completely disappeared, indicating a significant metabolic response.

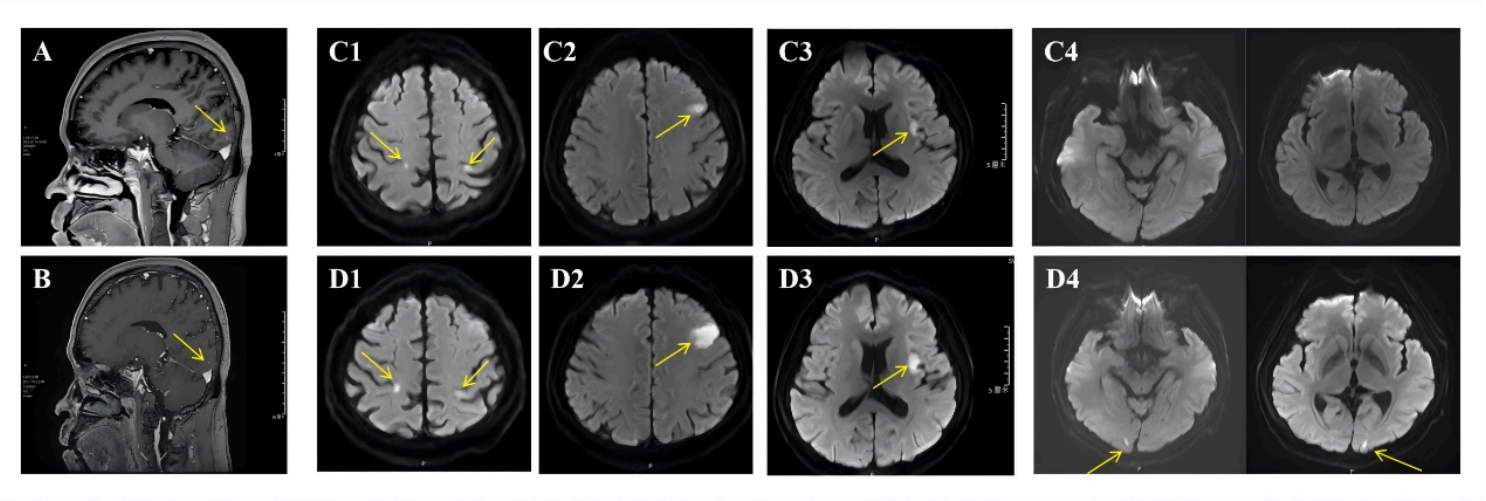


Figure 2

Longitudinal MRI assessment of intracranial metastatic progression. (A) Contrast-enhanced T1-weighted imaging (T1WI) (Dec 2023) shows a suspicious metastatic lesion in the right occipital lobe. **(B)** Diffusion-weighted imaging (DWI) (Feb 2024) shows the resolution of the previously seen abnormal enhancement in the right occipital lobe. **(C)** DWI (May 2024) reveals multiple hyperintense nodules in the subcortical regions of the bilateral parietal lobes (C1), left frontal lobe (C2), and left insular lobe (C3), with no abnormalities observed in the occipital lobes (C4). **(D)** Follow-up DWI (Jul 2024) demonstrates that the lesions in the bilateral parietal (D1), left frontal (D2), and left insular (D3) lobes have increased in size compared with the previous scan; additionally, new-onset hyperintense nodules (D4) are identified in the bilateral occipital lobes.

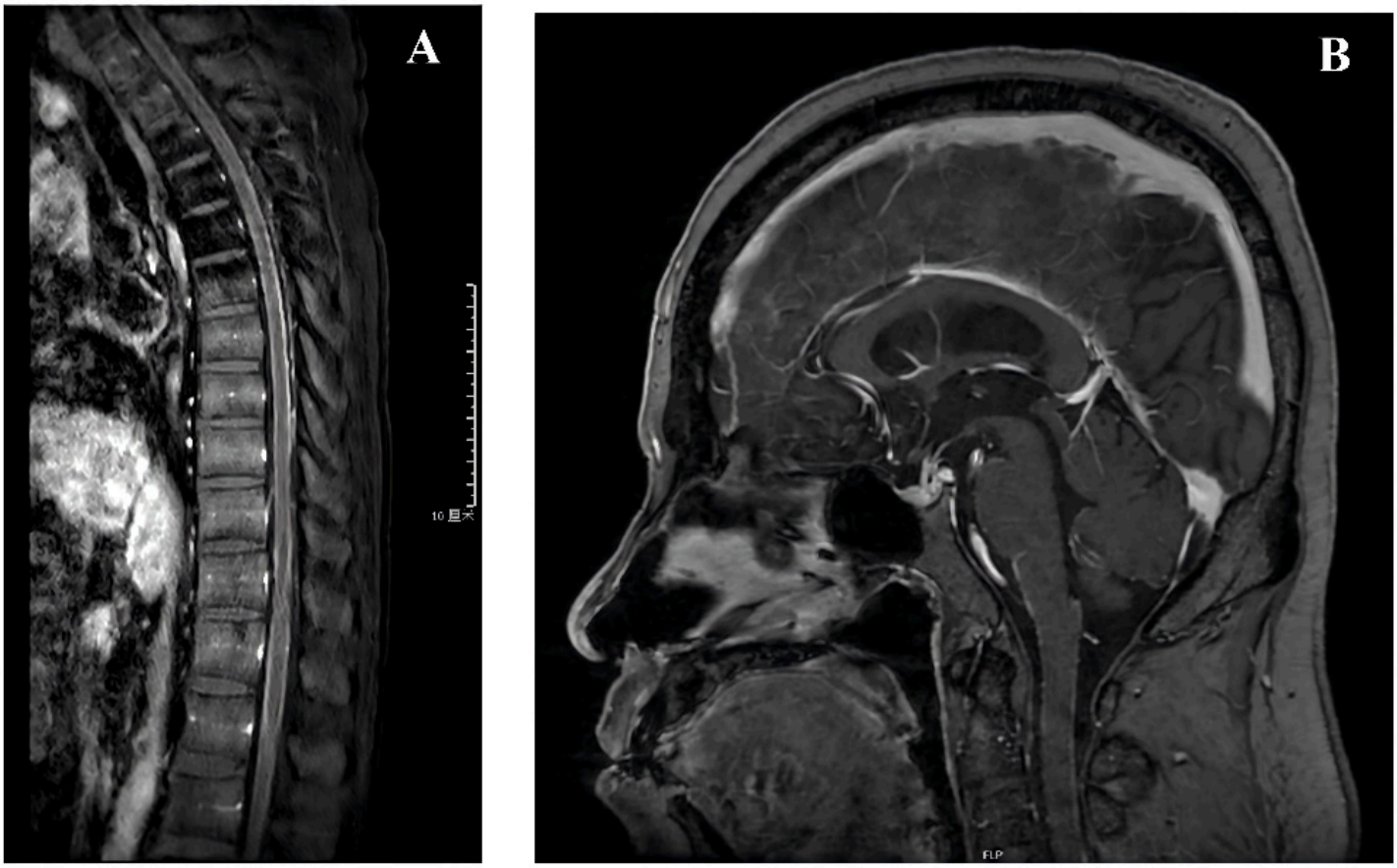


Figure 3

Contrast-enhanced MRI of the neuraxis (February 2025). (A) Sagittal contrast-enhanced MRI of the spine demonstrates heterogeneous intramedullary enhancement within the thoracic and lumbar spinal cord, accompanied by linear leptomeningeal enhancement. **(B)**Contrast-enhanced cranial MRI reveals heterogeneous enhancement along the meninges of the medulla oblongata.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CAREchecklist.pdf