OncoTargets and Therapy

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CASE REPORT

Fatal Steroid-Refractory Autoimmune Encephalitis Following Sequential Immune Checkpoint Inhibitor Therapy in Squamous Non-Small Cell Lung Cancer

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Abstract: Immune checkpoint inhibitors (ICIs) have improved outcomes in advanced non-small cell lung cancer (NSCLC) but can cause severe immune-related adverse events. We report a fatal case of suspected steroid-refractory autoimmune encephalitis in a 71-year-old male with squamous NSCLC, occurring 14 months after sequential ICI therapy (toripalimab, then sintilimab, followed by anlotinib-sintilimab). He presented with acute behavioral decline. Brain MRI revealed non-enhancing T2/FLAIR hyperintensities in the cerebellum and frontal lobes, with low cerebrospinal fluid (CSF) opening pressure. Diagnostic workup was negative for infections and neuronal autoantibodies. Despite aggressive immunosuppression with high-dose corticosteroids, mycophenolate mofetil, and intravenous immunoglobulin, his condition progressed to coma with diffuse cerebral edema and hydrocephalus, leading to death within 14 days. This case highlights the lethal potential of ICI-induced encephalitis, the diagnostic challenges of seronegative presentations, and the urgent need for more effective treatment strategies.

Keywords: immune checkpoint inhibitors, autoimmune encephalitis, steroid-refractory, neurotoxicity, NSCLC

Introduction

Immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 and CTLA-4 pathways have revolutionized the management of advanced non-small cell lung cancer (NSCLC), demonstrating significant survival benefits in both metastatic and locally advanced settings.[1,2] However, their immune-enhancing mechanisms can trigger immune-related adverse events (irAEs) affecting multiple organ systems, with neurological complications occurring in 1–12% of patients.[3] Among these, ICI-associated autoimmune encephalitis represents a rare but potentially fatal neurotoxicity, carrying a mortality rate exceeding 15% despite aggressive immunosuppression.[4,5] However, data detailing the risk and clinical characteristics of autoimmune encephalitis specifically following sequential ICI regimens remain particularly scarce. Furthermore, the expanding use of ICIs in NSCLC underscores the need for continued research into predictive biomarkers and novel analytical approaches to better understand and manage both their efficacy and toxicity profiles.[6,7]

The diagnosis of ICI-triggered encephalitis remains clinically challenging due to: (1) heterogeneous manifestations ranging from subtle behavioral changes to coma; (2) frequent absence of specific neuronal autoantibodies; (3) radiographic features overlapping with metastasis, infection, or vascular insults; and (4) lack of validated diagnostic biomarkers.[3,5,8] Current management relies heavily on corticosteroid escalation and intravenous immunoglobulin (IVIG), yet approximately 30% of cases prove steroid-refractory, requiring second-line agents like mycophenolate

Received: 8 August 2025
Accepted: 27 November 2025
Published: 4 December 2025

mofetil or rituximab.[5,9] The pathophysiological mechanisms—whether paraneoplastic, directly ICI-mediated, or synergistic with concomitant therapies-remain incompletely elucidated.[10]

We present a fatal case of steroid-refractory autoimmune encephalitis developing during sequential ICI therapy (toripalimab to sintilimab to anlotinib-sintilimab combination) in a patient with surgically resected squamous cell NSCLC. This case exemplifies critical clinical challenges: (1) delayed neurotoxicity onset after multiple ICI exposures; (2) diagnostic ambiguity despite exhaustive exclusion of infectious, metastatic, and vascular etiologies; and (3) rapid progression despite dual immunosuppression with corticosteroids and mycophenolate. This report underscores the fulminant potential of ICI-associated encephalitis and highlights unmet needs in risk stratification and therapeutic management.

Case Presentation

A 71-year-old Chinese male with an 80 pack-year smoking history (ceased at diagnosis) presented to Quzhou Hospital of Traditional Chinese Medicine on February 18, 2023, with a persistent cough lasting over two months. Chest computed tomography (CT) revealed a right lung mass suspicious for malignancy. Bronchoscopic biopsy confirmed moderately differentiated squamous cell carcinoma (immunohistochemistry: CK5/6+, P40+, P63+, TTF-1−). Staging evaluations (abdominal contrast-enhanced CT, brain magnetic resonance imaging (MRI)) showed no distant metastases, classifying the disease as cT3N2M0 (Stage IIIB NSCLC). He received two cycles of neoadjuvant therapy (toripalimab 200 mg once on day 1, nab-paclitaxel 300 mg once on day 1, nedaplatin 100 mg once on day 1; every 21 days) followed by right upper lobectomy at Zhejiang Cancer Hospital in April 2023. Pathological examination revealed residual squamous cell carcinoma (15×15×10 mm) with perineural invasion, lymphovascular invasion, and nodal metastases (station 4: 1/5; hilar: 2/7). Postoperatively, he completed two adjuvant cycles of the same regimen, followed by toripalimab maintenance (200 mg once on day 1, every 21 days).

In August 2023, surveillance PET-CT demonstrated disease progression with new FDG-avid lesions in the right hilum, mediastinal nodes (stations 2R/4R/7/8), liver segment IV, and right proximal femur. The patient subsequently enrolled in an investigator-initiated trial combining anlotinib (12 mg days 1–14, every 21 days) and sintilimab (200 mg once on day 1, every 21 days). Immune-related pneumonitis developed in December 2023, prompting discontinuation of sintilimab. Anlotinib monotherapy was continued with radiologically stable disease.

On April 8, 2024, he presented to our hospital with 1 week of progressive fatigue and behavioral changes. Brain MRI demonstrated new non-enhancing punctate and patchy T2/FLAIR hyperintensities in the cerebellar vermis and bilateral frontal lobes (Figure 1A–1D), inconsistent with metastatic disease. Serum evaluations (thyroid function, cortisol, electrolytes) were unremarkable. Comprehensive CSF testing excluded infectious (bacterial/fungal cultures, cryptococcal antigen, GeneXpert MTB/RIF, metagenomic next generation sequencing (NGS)) and autoimmune etiologies (autoimmune/paraneoplastic antibody panels) (Table 1). PET-CT suggested cerebral infarction (Figure 1E–1H), but MR angiography ruled out vascular occlusion. Automated 3D echocardiography revealed reduced left ventricular global longitudinal strain (−10.7%), suggesting subclinical myocardial injury (Figure 2), though troponin levels remained normal. Lumbar puncture showed low opening pressure (50 mm H_2O) with normal cerebrospinal fluid (CSF) biochemistry and cytology. Given the history of immune-related pneumonitis and cardiac dysfunction, immune checkpoint inhibitor-associated encephalitis was suspected.

Initial management included intravenous methylprednisolone (2 mg/kg/day) and mycophenolate mofetil (1 g twice daily). After 1 week, the patient's consciousness deteriorated to coma. Repeat lumbar puncture still showed low opening pressure (60 mm H_2O) with persistently negative studies. A multidisciplinary consensus upheld the diagnosis of probable steroid-refractory ICI-related encephalitis. Therapy was escalated to pulse methylprednisolone (1000 mg/day for 3 days) and Immunoglobulin (IVIG) (20 g/day). Despite intervention, follow-up MRI on April 22, 2024, revealed extensive vasogenic edema, hydrocephalus, and diffuse T2 hyperintensities throughout the cerebrum, basal ganglia, brainstem, and cerebellum (Figure 3A–3D). The patient experienced rapid neurological decline and died 14 days after admission. A detailed timeline of the patient's treatment course is provided in Table 2. This case report was drafted in accordance with the CARE Checklist (Appendix 1).

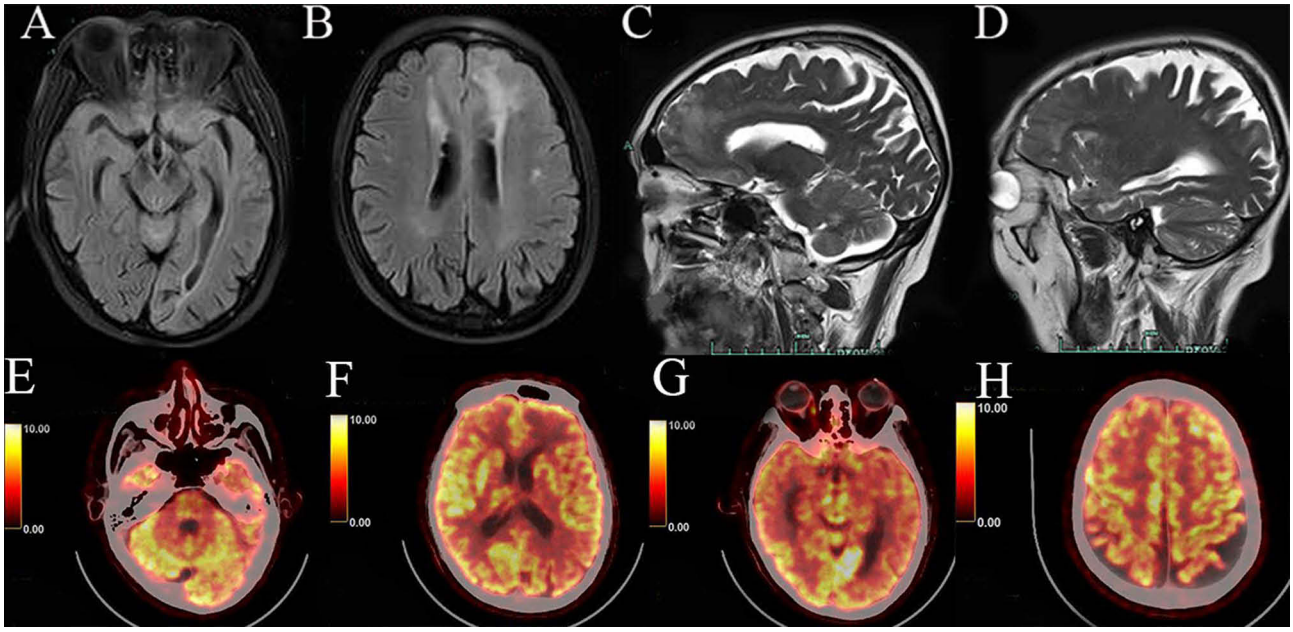

Figure 1 Brain MRI and PET-CT findings. (**A**) Initial axial T2-weighted FLAIR MRI (3T Siemens Magnetom Skyra; TR/TE/TI = 9000/90/2500 ms) at the level of the cerebellar vermis at symptom onset, showing non-enhancing punctate hyperintensities. Scale bar: 1 cm. (**B**) Initial axial T2-weighted FLAIR MRI (same parameters as (**A**) at a adjacent level of the cerebellar vermis, demonstrating patchy hyperintensities. Scale bar: 1 cm. (**C**) Initial axial T2-weighted FLAIR MRI (same parameters as (**A**) at the level of the frontal lobes, revealing punctate hyperintensities in the bilateral frontal subcortical white matter. Scale bar: 1 cm. (**D**) Initial axial T2-weighted FLAIR MRI (same parameters as (**A**) at a slightly higher level of the frontal lobes, showing confluent patchy hyperintensities. Scale bar: 1 cm. (**E**) Fused axial [^{18}F]FDG PET-CT image (GE Discovery Max+; 45–60 min post-injection; SUV scale 0–5) corresponding to the cerebellar level in (**A** and **E**), demonstrating marked hypometabolism in the vermis. Scale bar: 1 cm. (**F**) Fused axial [^{18}F]FDG PET-CT image corresponding to the cerebellar level in (**B** and **F**), confirming extensive cerebellar hypometabolism. Scale bar: 1 cm. (**G**) Fused axial [^{18}F]FDG PET-CT image corresponding to the frontal lobe level in (**C** and **G**), showing significant hypometabolism in the bilateral frontal cortices. Scale bar: 1 cm. (**H**) Fused axial [^{18}F] FDG PET-CT image corresponding to the frontal lobe level in (**D** and **H**), revealing widespread frontal cortical hypometabolism. Scale bar: 1 cm.

Discussion

To our knowledge, this is the first detailed report of fatal, probable steroid-refractory autoimmune encephalitis following a sequential regimen of toripalimab, then sintilimab, and finally anlotinib in combination with sintilimab in a patient with squamous NSCLC. This fatal case of steroid-refractory autoimmune encephalitis likely complicating sequential ICI therapy for squamous cell NSCLC underscores the diagnostic and therapeutic challenges of this rare neurotoxicity. Our patient developed rapidly progressive encephalitis 14 months after initial ICI exposure (toripalimab), with onset occurring during anlotinib-sintilimab combination therapy despite prior immune-related pneumonitis. This aligns with

Table 1 Cerebrospinal Fluid (CSF) Findings on April 11 and April 16, 2024

Parameter	April 11 Result	April 16 Result	Reference Range	Unit
Opening pressure	50	60	70–180	mmH_2O
Appearance	Colorless	Colorless	—	—
Clarity	Clear	Clear	—	—
Pandy test	±	±	Negative	—
Leukocyte count	20	20	0–8	/μL
Mononuclear cells	1.1	1.1	—	—
Cryptococcus	Not seen	Not seen	—	—
Erythrocyte count	150	50	0	/μL
Glucose	0.48	0.11	2.50–4.40	mmol/L
Chloride	118.7	118.9	120.0–130.0	mmol/L
Lactate dehydrogenase	697.2	1011.7	3.0–40.0	U/L
Total protein	0.71	1.33	0.20–0.40	g/L

https://doi.org/10.2147/OTT.S557750

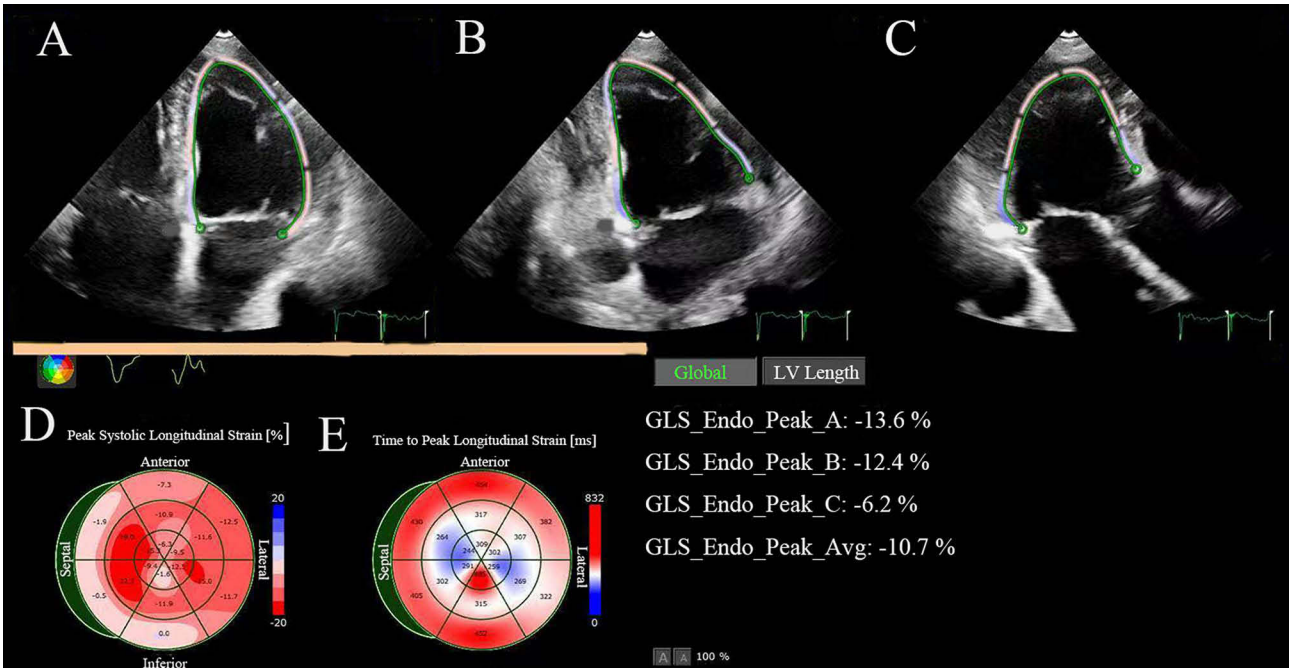

Figure 2 Speckle tracking echocardiography (STE) assessment of left ventricular global longitudinal strain (LVGLS). Images were acquired using a Philips EPIQ 7C ultrasound system with a S5-1 transducer (frequency range: 1.7–2.0 MHz). The tracking analysis was performed offline using QLAB version 13.0. (**A–C**) display the apical four-chamber (A4C; **A**), two-chamber (A2C; **B**), and three-chamber (A3C; **C**) views, respectively, with automated endocardial border tracking for longitudinal strain analysis throughout the cardiac cycle. (**D**) presents a bull's-eye plot summarizing the segmental peak systolic longitudinal strain values (%), while (**E**) shows the corresponding time-to-peak strain for each segment. The globally reduced LVGLS of −10.7% suggests subclinical left ventricular dysfunction.

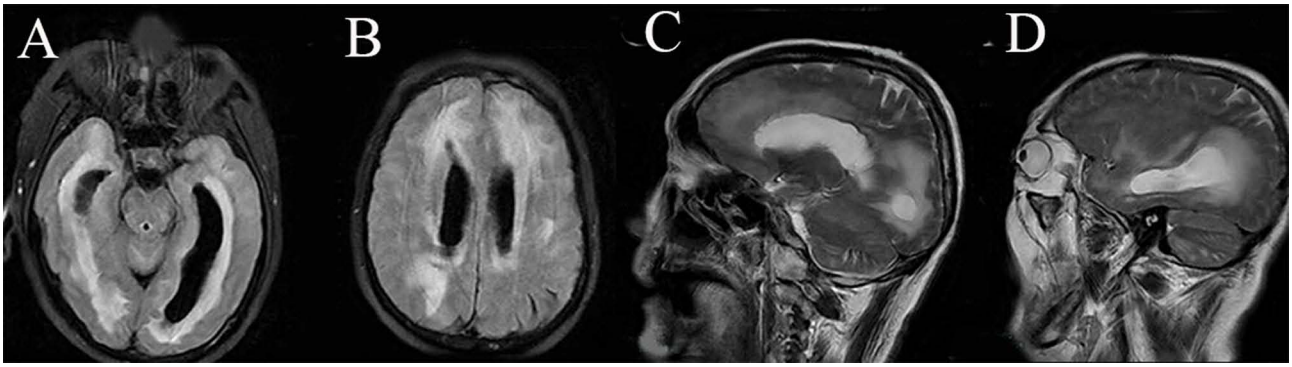

Figure 3 Brain MRI findings during disease progression. (**A**) Follow-up axial T2-weighted FLAIR MRI (same scanner and sequence) on day 14 at a level comparable to (**A**), revealing early effacement of sulci and hyperintensities in the cerebellar vermis. Scale bar: 1 cm. (**B**) Follow-up axial T2-weighted FLAIR MRI on day 14 at a level comparable to (**B**), showing progressive diffuse edema with marked sulcal effacement and widespread hyperintensities. Scale bar: 1 cm. (**C**) Follow-up axial T2-weighted FLAIR MRI on day 14 at a level comparable to (**C**), demonstrating extensive white matter hyperintensities and effacement of the frontal sulci. Scale bar: 1 cm. (**D**) Follow-up axial T2-weighted FLAIR MRI on day 14 at a level comparable to (**D**), showing severe diffuse cerebral edema with ventricular compression and confluent white matter hyperintensities. Scale bar: 1 cm.

literature suggesting delayed neurotoxicity may arise after multiple ICI courses or regimen switches, potentially reflecting cumulative immune dysregulation.[10]

Immune checkpoint inhibitor-induced autoimmune encephalitis, while representing a rare neurological irAE, carries significant morbidity and mortality. Its precise incidence remains difficult to ascertain but is estimated to be below 1%, substantially lower than the frequency of other neurological irAEs such as myositis or neuropathy.[11,12] However, this rarity contrasts sharply with its clinical impact. Reported mortality rates for ICI-associated encephalitis are notably high, emphasizing the critical importance of early recognition and intervention, as illustrated by the fatal outcome in the present case despite aggressive immunosuppressive therapy.

Table 2 Timeline of Treatment and Clinical Course

Treatment Phase	Dates	Regimen (Dosage)	Number of Cycles	Reason for Discontinuation
Neoadjuvant Therapy	Feb, 2023	Toripalimab (200 mg, d1) + Nab-paclitaxel (300 mg, d1) + Nedaplatin (100 mg, d1), Q3W	2 cycles	Completed as planned. Proceeded to surgery.
Surgery	Apr, 2023	Right upper lobectomy and lymph node dissection.	-	Pathological staging: ypT2aN0M0.
Adjuvant Therapy	May, 2023	Toripalimab (200 mg, d1) + Nab-paclitaxel (300 mg, d1) + Nedaplatin (100 mg, d1), Q3W for 2 cycles, followed by Toripalimab (200 mg, d1), Q3W for 2 cycles	4 cycles	Development of immune-related pneumonia (Grade 2). Toripalimab was permanently discontinued.
Treatment-Free Interval		Best supportive care	-	Chest CT showed improvement of pneumonia. No anticancer therapy.
Disease Progression	Aug, 2023	Imaging confirmed disease recurrence.	-	-
First-Line for Metastatic Disease	Aug, 2023	Sintilimab (200 mg, d1) + Anlotinib (12 mg, d1-14), Q3W	4 cycles	Sintilimab-related pneumonia (Grade 2). Sintilimab was permanently discontinued.; Anlotinib was continued as maintenance.
Maintenance Therapy	Dec, 2023	Anlotinib (12 mg, d1–14), Q3W	4 cycles	
Neurological Symptom Onset	Apr, 2024	The patient presented with acute neurological decline.	-	Marked as the onset of suspected autoimmune encephalitis.

The diagnosis remained elusive despite exhaustive investigations. Brain MRI revealed non-enhancing T2/FLAIR hyperintensities in cerebellar vermis and frontal lobes (Figure 1A–1D), inconsistent with metastatic patterns but resembling vasogenic edema reported in ICI-associated encephalitis.[8,13] CSF analyses showed low opening pressure (50–60 mm H_2O) but otherwise normal cytology/biochemistry, paralleling cases where CSF abnormalities are absent despite severe neurological involvement.[14] Critically, comprehensive autoimmune/paraneoplastic antibody panels (including anti-Ma2, Hu, NMDAR) were negative, echoing observations by Vogrig et al that approximately 40% of ICI-triggered encephalitis cases lack identifiable neuronal antibodies.[4] This seronegativity complicates differentiation from vascular/infectious mimics, as evidenced by PET-CT initially suggesting infarction (Figure 1E–1H).

Beyond reiterating the established association between ICIs and encephalitis, our case compels a deeper inquiry into the mechanisms underlying its peculiarly aggressive and refractory nature. We hypothesize that the sequential administration of two different anti-PD-1 agents may have led to a cumulative T-cell activation, potentially targeting a broader repertoire of antigens and culminating in an overwhelming CNS inflammatory response. The seronegative status further complicates the picture, suggesting that the immune response may be directed against neuronal antigens not covered by conventional commercial panels or may be primarily T-cell mediated, a pathology not detectable by standard antibody assays. Notably, the addition of anlotinib, a multi-target tyrosine kinase inhibitor with anti-angiogenic activity, warrants special consideration. It is plausible that anlotinib, by altering the tumor microenvironment and vascular permeability, may have paradoxically enhanced T-cell trafficking across the blood-brain barrier or amplified the pre-existing immune activation triggered by the prior ICIs, thereby accelerating the neuroinflammatory cascade. This hypothesis, while speculative, highlights a critical gap in our understanding of the interplay between anti-angiogenic agents and ICI toxicity. Future studies should prioritize cytokine profiling in such cases to identify potential drivers of this hyperacute phenotype and explore the potential of early, targeted immunosuppression other than corticosteroids.

Therapeutic failure despite dual immunosuppression highlights the aggressive nature of this suspected entity. Initial methylprednisolone (2 mg/kg/day) plus mycophenolate mofetil failed to halt neurological decline, mirroring steroid-refractory cases in NSCLC literature where mortality exceeds 30%.[5,15] Escalation to pulse steroids and IVIG (20 g/day) also proved ineffective, consistent with reports by Schneider et al and Leitinger et al describing fatal outcomes despite

multimodal therapy.[9,15] This contrasts with the favorable prognosis in Wang et al's case,[16] emphasizing that encephalitis severity varies substantially across patients. Potential contributors to treatment resistance in our case include: (1) Concomitant tyrosine kinase inhibitor (anlotinib): Synergistic immunomodulatory effects may have exacerbated neuroinflammation.[3] (2) Pre-existing cardiac involvement: Subclinical myocardial injury (reduced LV-GLS) suggests multi-organ irAEs, associated with poorer neurological outcomes.[17] (3) Delayed intervention: Encephalitis diagnosis occurred >1 week after symptom onset, reducing therapeutic window efficacy.[16]

The therapeutic management of this case was guided by established guidelines for severe neurological irAEs, yet the rapid, fulminant clinical course posed significant challenges. The initial escalation to high-dose corticosteroids combined with mycophenolate mofetil represented an aggressive attempt to control the suspected immune-mediated process. However, the rationale for subsequently prioritizing intravenous immunoglobulin (IVIG) over alternatives such as rituximab or tocilizumab was primarily dictated by the urgency of the situation. The patient's neurological status deteriorated to coma within a week of symptom onset, leaving a critically narrow therapeutic window. Agents like rituximab, which typically require weeks to achieve maximal B-cell depletion and clinical effect, were deemed unlikely to yield a timely response in this hyperacute context. Similarly, while plasmapheresis was considered, the patient's evolving hemodynamic instability and signs of increased intracranial pressure rendered this intervention high-risk. The failure of pulse steroids and IVIG underscores the formidable challenge posed by this steroid-refractory, rapidly progressive variant of ICI-encephalitis. This experience highlights the critical need for both predictive biomarkers to identify patients at risk for such fulminant courses and the exploration of novel, rapidly-acting immunomodulatory strategies for these critical scenarios where conventional escalation protocols fail.

The attribution of encephalitis to ICIs in this case requires careful consideration of two key factors: the temporal relationship and potential confounding by concomitant medication. The onset of neurological symptoms approximately four months after the last dose of sintilimab represents an atypically delayed presentation, which may challenge a direct causal link. However, well-documented cases of delayed neurological irAEs, occurring months after ICI cessation, support the possibility of a smoldering immune activation that eventually culminated in overt encephalitis. Furthermore, the potential role of anlotinib must be acknowledged as a significant confounding factor. As a multi-targeted anti-angiogenic agent, anlotinib may have directly influenced the central nervous system microenvironment, potentially by altering blood-brain barrier permeability and facilitating the trafficking of activated immune cells. It is plausible that anlotinib acted synergistically with the pre-existing immune dysregulation caused by the sequential ICIs, thereby precipitating or amplifying the neuroinflammatory cascade. Therefore, while the sequential ICI regimen is considered the most probable culprit, a synergistic effect with anlotinib or even a primary insult by the TKI cannot be entirely ruled out. This diagnostic uncertainty underscores the complex interplay between different anticancer agents and highlights the critical need for a high index of suspicion for such rare, yet devastating, toxicities even long after ICI discontinuation and during subsequent lines of therapy.

Limitations include the inability to perform postmortem neuropathological analysis to confirm autoimmune-mediated neuronal injury. Moreover, we regret that a comprehensive serum autoantibody panel was unavailable at our institution due to technical constraints at the time of the patient's presentation. Furthermore, cytokine profiling of the CSF (eg, IL-6, TNF-α) was not performed, representing a potential avenue for future biomarker investigation in similar cases. Additionally, while CSF metagenomic NGS excluded common pathogens, rare/atypical infections cannot be definitively ruled out.

Conclusion

This case illustrates the lethal potential of probable autoimmune encephalitis in patients receiving sequential or combination ICI regimens. Seronegativity and nonspecific imaging findings suggest that a high index of clinical suspicion is warranted, even in the absence of conventional biomarkers. In steroid-refractory cases, earlier escalation to alternative immunosuppressive agents (eg, rituximab or IL-6 inhibitors) might be considered, as suggested by emerging evidence and expert consensus for managing severe neurological irAEs[18,19], though supporting evidence from large-scale trials is still limited. The challenges encountered in this case highlight several important needs for the field: (1) the development of multinational or multicenter registries to better characterize severe neurological irAEs; (2)

further research into biomarkers, including proteomic and cytokine profiling, to improve early diagnosis; and (3) clinical trials to evaluate the efficacy of second-line immunosuppressants. Future studies that incorporate variables such as prior irAEs and ICI exposure duration may help guide the management of this serious complication.

Data Sharing Statement

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

Ethics Statements

The publication of the present case details was approved by Ethical Committee of People′s Hospital of Quzhou.

Acknowledgments

In accordance with our hospital's standard protocol and journal policy, written informed consent was obtained from the deceased patient's next-of-kin for the publication of the case details and accompanying images. The consent form explicitly authorized the use of clinical data for scientific research and publication purposes, with strict anonymization and protection of privacy.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The study was supported by Science and Technology Key Project of Quzhou (2022K48), "New 115" Talent Project of Quzh ou, "551" Health High-level Talents of Zhejiang Province, and "258" Talent Project of Quzhou.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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