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Nivolumab-induced Limbic Encephalitis in Gastric Cancer: A Case Report and Literature Review

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Abstract

Background/Aim: Immune checkpoint inhibitors (ICIs), including nivolumab, have markedly improved gastric cancer (GC) outcomes. However, immune-related adverse events involving the central nervous system are rare and potentially life-threatening. Limbic encephalitis is an exceptionally uncommon manifestation, and its clinical course remains poorly understood. We conducted a literature review of ICI-induced encephalitis specifically in patients with gastrointestinal cancers to clarify its clinical characteristics and management.

Case Report: We describe the case of an 83-year-old man with unresectable advanced GC who received multiple lines of chemotherapy, including nivolumab as third-line therapy. After more than 40 cycles of nivolumab treatment, the patient developed progressive cognitive decline. Brain magnetic resonance imaging (MRI) revealed fluid attenuated inversion recovery hyperintensity in the right hippocampus, consistent with limbic encephalitis. Nivolumab was discontinued without corticosteroid administration, leading to gradual cognitive recovery. Follow-up MRI demonstrated resolution of hippocampal abnormalities.

Conclusion: This case highlights an exceptionally rare instance of nivolumab-induced limbic encephalitis in a patient with GC. While our patient recovered spontaneously after drug discontinuation without corticosteroids, the key clinical implication is that new-onset cognitive decline in elderly patients receiving ICIs should not be misattributed to dementia progression. Early recognition of neurological immune-related adverse events is essential, as continued ICI therapy in unrecognized cases may result in irreversible or even fatal outcomes.

Keywords: Gastric cancer, encephalitis, nivolumab, case report.

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the management of various malignancies, including gastric cancer (GC). The phase III ATTRACTION-2 trial established nivolumab, a programmed death-1 inhibitor, as an effective third-line treatment option, demonstrating an overall survival benefit in heavily pretreated patients

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(1). Since then, subsequent studies have expanded the role of ICIs, and nivolumab is now incorporated into first-line treatment regimens for unresectable or recurrent advanced GC (2, 3), with ongoing research into predictive biomarkers for its efficacy (4).

Despite their clinical efficacy, ICIs are associated with a unique spectrum of immune-related adverse events (irAEs) that can affect multiple organs. Neurological irAEs are relatively rare, occurring in 1-5% of patients, but they encompass a broad range of potentially life-threatening presentations (5, 6). Among these, limbic encephalitis is an especially uncommon entity. ICI-induced encephalitis can range from fully reversible to fatal types (7). Recent reports have further characterized the clinical features, management, and prognosis of nivolumab-induced immune encephalitis, highlighting its variable clinical course and diagnostic challenges (8).

The characteristic features of ICI-related limbic encephalitis include cognitive decline, memory impairment, behavioral changes, seizures, and MRI findings of hippocampal hyperintensity. Most reported cases require high-dose corticosteroid therapy, and most have been described in patients with melanoma, lung cancer, or renal cell carcinoma (9). However, reports on GC are scarce.

Herein, we describe the case of an elderly patient with unresectable advanced GC who developed nivolumab-associated limbic encephalitis after prolonged treatment.

Case Report

An 83-year-old man presented with unresectable advanced gastric cardia adenocarcinoma, characterized by para-aortic lymph node metastases and direct invasion of the left lobe of the liver and diaphragm. He was initially treated with systemic chemotherapy including fluoropyrimidine and platinum-based regimens. His medical history included hypertension and hyperuricemia, for which he was receiving candesartan, manidipine, allopurinol, and ethyl icosapentate. He had no known drug allergies and maintained an Eastern Cooperative Oncology Group performance status score of 0 at the time of treatment initiation. In accordance with the treatment guidelines at that time, nivolumab monotherapy was introduced as third-line therapy following disease progression (10). After the 40th course of nivolumab (approximately 18 months after the therapy initiation), the patient developed acute disorientation, short-term memory loss, and behavioral changes, leading to a referral to the department of neurology.

Brain magnetic resonance imaging (MRI) revealed hyperintense signals in the right hippocampus on T2-weighted and fluid attenuated inversion recovery (FLAIR) images, consistent with limbic encephalitis (Figure 1A). There was no evidence of brain metastases, cerebrovascular events, or intracranial infection. The routine laboratory findings were unremarkable. Cerebrospinal fluid examination, neuronal autoantibody testing, and formal neuropsychological assessment were not performed, given the mild nature of the symptoms and their rapid clinical improvement.

Given the temporal association between nivolumab therapy and characteristic radiographic findings, immune checkpoint inhibitor–related limbic encephalitis was strongly suspected. GC also progressed, so nivolumab was discontinued. As his neurological symptoms were relatively mild and spontaneously improved after drug withdrawal, high-dose corticosteroid therapy was not initiated. Within several weeks, his cognitive and behavioral symptoms resolved, and a follow-up MRI obtained three months later demonstrated gradual resolution of the temporal lobe abnormalities (Figure 1B).

The patient subsequently underwent, trifluridine/tipiracil chemotherapy. During this treatment course, palliative radiotherapy was administered to mediastinal lymph nodes that compressed the superior vena cava. Later, as para-aortic lymph nodes enlarged, additional radiotherapy was delivered. Neurological symptoms did not recur during further oncological treatment. Approximately one year after the discontinuation of nivolumab, the patient died of progressive GC.

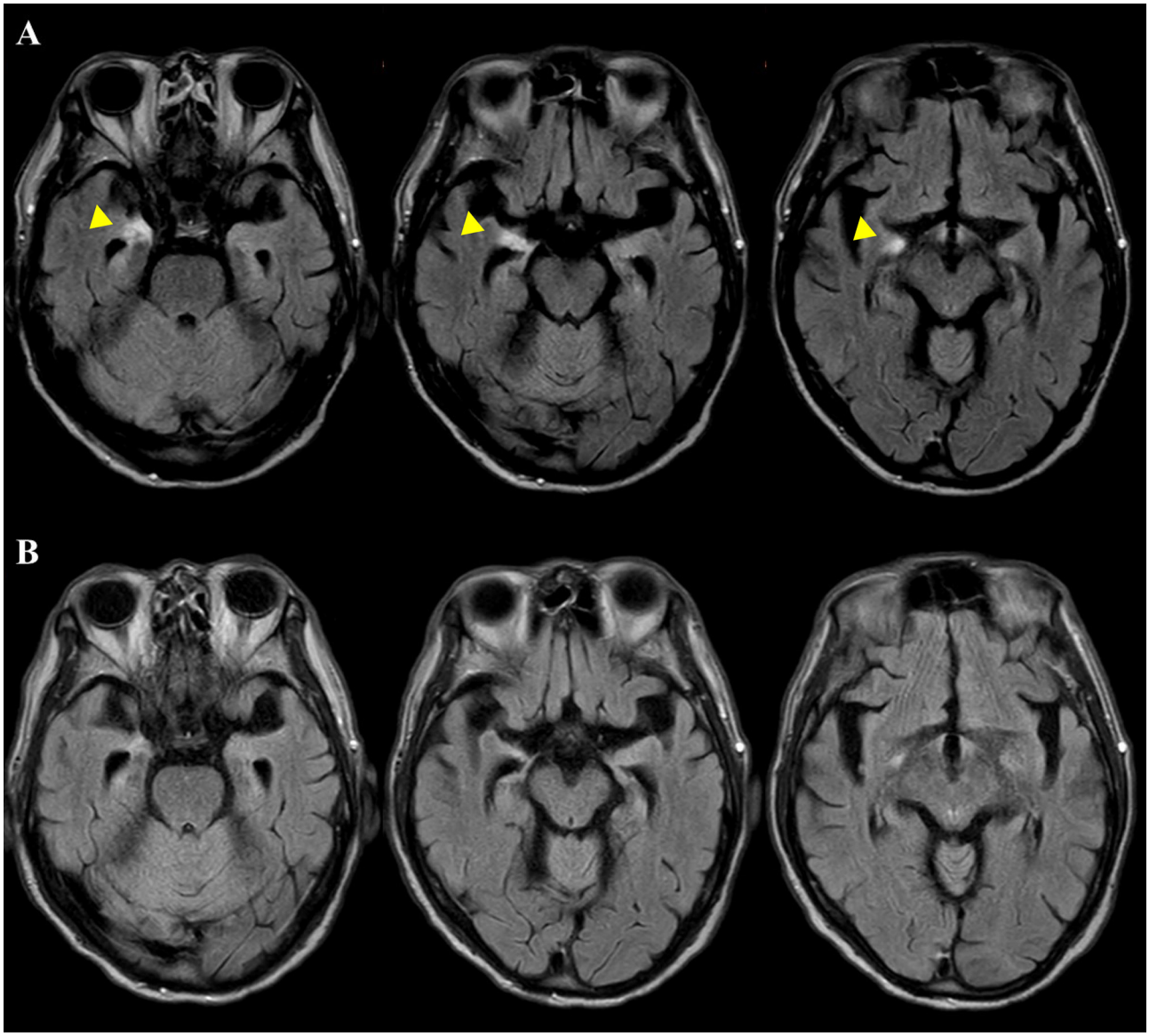

Figure 1. *Brain magnetic resonance imaging (MRI) findings of nivolumab-associated limbic encephalitis. (A) Axial fluid attenuated inversion recovery (FLAIR) image at the time of symptom onset showing hyperintense signal in the right hippocampus, consistent with limbic encephalitis (yellow arrow). (B) Follow-up MRI obtained three months after nivolumab discontinuation demonstrating resolution of the hippocampal hyperintensity, corresponding with clinical improvement of cognitive symptoms.*

Discussion

ICIs have significantly improved the prognosis of patients with advanced cancers, including GC. However, they are also associated with irAEs in various organs. Neurological irAEs are relatively rare, accounting for less than 5% of ICI-treated patients but can present with diverse and potentially severe manifestations (5-7). However, limbic encephalitis is uncommon.

Previous reports on nivolumab-associated limbic encephalitis primarily involved patients with melanoma, non-small cell lung cancer, and renal cell carcinoma

Table I. *Summary of reported cases of immune checkpoint inhibitor-induced encephalitis in patients with gastrointestinal cancers.*

Author (Year)	Cancer type	ICI agent	Onset	Main symptoms	MRI findings	Treatment	Outcome
Laderman *et al.* (2022) (9)	GEJ	Pembrolizumab	4 cycles	Cognitive dysfunction	High intensity in the hippocampus	Steroids	Improved
Tani *et al.* (2022) (10)	GEJ	Nivolumab	2 cycles	Disturbance of consciousness	Normal	Steroids	Improved
Present Case (2026)	GC	Nivolumab	40 cycles	Cognitive dysfunction	High intensity in the hippocampus	None	Improved

GEJ: Gastroesophageal cancer; GC: gastric cancer; ICI: immune checkpoint inhibitor; MRI: magnetic resonance imaging.

(9). As summarized in Table I, reported cases of ICI-induced encephalitis in gastrointestinal cancers are extremely limited (11, 12). A literature search identified only two cases involving the gastroesophageal junction cancer. In these cases, limbic encephalitis occurred relatively early (within 2-4 cycles) and required high-dose corticosteroids for recovery, whereas our case is uniquely characterized by its extremely late onset after 40 cycles and spontaneous improvement without steroids. We report the first description of this complication in a patient with GC treated with nivolumab, underscoring not only its extreme rarity but also the need for vigilance, particularly in elderly patients. In this population, new-onset cognitive decline may be misattributed to dementia progression, risking delayed recognition of a potentially reversible irAE.

The diagnosis of ICI-related limbic encephalitis remains challenging because clinical features such as acute confusion, short-term memory loss, and behavioral changes may mimic paraneoplastic syndromes, infectious encephalitis, or brain metastases. In elderly patients, there is an additional concern that these symptoms could be mistaken for underlying cognitive decline. MRI findings of bilateral medial temporal lobe hyperintensities are characteristic; however, antibody testing against neuronal antigens, cerebrospinal fluid analysis, and electroencephalography may be helpful in excluding other etiologies (13). In this case, antibody testing was not performed, which is a limitation of this study. Nevertheless, the temporal association between nivolumab and the clinical course supported the diagnosis.

Reports indicate that the majority of patients required high-dose corticosteroids, and some also needed additional immunosuppressive therapies (4, 6). In patients with advanced GC treated with ICIs, the occurrence of irAEs has been reported to be associated with clinical outcomes, highlighting the importance of careful monitoring and appropriate management of these events (14). In contrast, our patient achieved complete recovery without steroid treatment, suggesting that ICI withdrawal alone may be sufficient in selected cases. However, given the potential for fulminant disease progression, prompt recognition and early intervention are essential. Further case studies are required to define the optimal management strategy for this rare complication.

Conclusion

We report an exceptionally rare case of nivolumab-induced limbic encephalitis in a patient with unresectable advanced GC. Distinctive features include late onset after long-term therapy and spontaneous recovery following drug withdrawal without corticosteroid treatment. These findings emphasize that neurological irAEs may occur at any stage of ICI therapy and that the spectrum of severity is wider than previously recognized. Awareness of this entity is crucial for early diagnosis, timely management, and informed decision making regarding the continuation of immunotherapy in patients with GC, particularly in elderly patients who may present with subtle or atypical neurological symptoms.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Shutaro Sumiyoshi drafted the manuscript. Shutaro Sumiyoshi, Takeshi Kubota, Hiroyuki Inoue, Kazuya Takabatake, Keiji Nishibeppu, Toshiyuki Kosuga, Hirotaka Konishi, Hitoshi Fujiwara, and Atsushi Shiozaki performed dedicated reviews and contributed to the discussion. All the Authors have read and approved the final version of the manuscript.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the Authors.

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