Hope, Cure, and Adverse Effects in Immunotherapy: Atezolizumab-Associated Encephalitis in Metastatic Small Cell Lung Cancer – A Case Report and Literature Review

Eiman Y. Ibrahim  Weige Charlie Zhao  Haritha Mopuru  Christopher Janowiecki  David J. Regelmann

Internal Medicine Residency Program, Quinnipiac University Frank H. Netter MD School of Medicine, St. Vincent’s Medical Center, Bridgeport, CT, USA

Keywords
Cancer · Atezolizumab · Encephalitis · Immunotherapy · Immune checkpoint inhibitors

Abstract
Cancer immunotherapies have been revolutionary treatments in oncological disease. Such therapies include immune checkpoint inhibitors that target programmed cell death protein, ligands, and cytotoxic T-lymphocyte-associated antigen (CTLA-4). Increased use has led to recognition of immune-related adverse events. Such events are often distinct from the typical adverse events of traditional cancer therapies. Immune-related adverse events are more commonly found to affect the skin, gastrointestinal tract, and endocrine system. The incidence of these adverse events remains low for central nervous system effects. This article describes a case of atezolizumab-associated encephalitis in a patient with metastatic small cell lung cancer.

Introduction
Clinicians increasingly use immune checkpoint inhibitors as immunotherapies in oncological disease. Several immune checkpoint inhibitors, including nivolumab, pembrolizumab, durvalumab, and atezolizumab, are now approved for the treatment of breast, melanoma,
urological, colorectal cancers, and lymphoma [1]. These agents have shown outstanding efficacy in the treatment of advanced solid tumors through targeting intrinsic immunosuppressive checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) as well as programmed cell death protein and ligands (PD-L) 1 and 2. The resulting effect eliminates neoplastic inhibition of the immune response against tumor cells, leading to reversal of peripheral tolerance. The most common adverse effects of these therapies are fatigue, rash, and gastrointestinal symptoms. Central nervous system toxicity is relatively uncommon [2]. This article describes a case of a 71-year-old female who received the anti-PD-L1 agent atezolizumab for 4 months and was found to have atezolizumab-induced encephalitis (AIE).

**Case**

A 71-year-old female with extensive small cell lung cancer (Fig. 1) and brain metastasis underwent active treatment for her malignancy. Her prior therapy included four cycles of carboplatin/etoposide chemotherapy. She was then transitioned to maintenance therapy with atezolizumab every 3 weeks for the 4 months prior to presentation. She arrived at her infusion center for her scheduled treatment with altered mentation, prompting transportation to the emergency department, and hospital admission.

On arrival, the patient's vital signs were within normal limits. Neurological examination did not elicit any focal findings but was significant for lethargy, disorientation, and cognitive slowing. Magnetic resonance imaging brain scan with and without contrast showed no evidence of acute pathology (Fig. 2). Long-term 48-h continuous EEG monitoring was unremarkable for evidence of electrographic seizures or of epileptiform discharges. Cerebrospinal fluid (CSF) showed lymphocytic pleocytosis (white blood cell 510/µL, 95% lymphocytes), elevated protein (447 mg/dL), and glucose of 62 mg/dL. CSF cultures were negative, as were quantitative viral testing on the serum and CSF. CSF cytology did not reveal malignant cells. The treating team suspected AIE, and the patient received treatment with high-dose systemic steroids. Within 10 days of steroid treatment, she had marked clinical response in cognition, which continued to improve throughout her hospitalization. She was discharged to home from the hospital to continue her neurologic recovery.

**Discussion**

Though effective in the treatment of many cancers, immune checkpoint inhibitors are associated with a variety of immune-related adverse events [3]. Encephalitis induced by atezolizumab is rare. In the OAK trial (atezolizumab vs. docetaxel in previously treated nonsmall cell lung cancer [NSCLC]), encephalitis was reported in 5 of 609 patients in the atezolizumab arm [4]. Subsequently, cases of AIE have been reported in the literature (Table 1).

![Fig. 1. Axial CT image of the chest demonstrating a 1.5 cm left lower lobe lung mass (red arrow).](image-url)
As noted, the majority of the patients included in this table were diagnosed with NSCLC. Nonetheless, there have been no detailed explanations of encephalitis mediated by atezolizumab in patients with NSCLC in the cited literature. Possible factors could be the widespread use of atezolizumab monotherapy in the treatment of metastatic NSCLC with high expression of PD-L1 in comparison to platinum-based combination chemotherapy among this patient population [11]. Atezolizumab also demonstrated a satisfactory safety profile and promising survival benefit in patients with NSCLC who had asymptomatic or clinically stable brain metastases [12]. The mechanisms underlying this relationship are unclear and might be attributed to pharmacological factors, including the duration and dosage of atezolizumab as well as molecular factors including the presence of preexisting infiltrating lymphocytes, tumor mutational burden, and defective antigen presentation. Future research should focus on elucidating the possible mechanisms for interactions of atezolizumab with tumor immune microenvironment in NSCLC.

In many of atezolizumab-associated encephalitis cases, the onset of symptoms occurred approximately 2 weeks after initiation of immunotherapy. Our patient differs as she received 4 months of therapy prior to manifesting clinically significant adverse effects. Magnetic resonance imaging results in these cases, consistent with our patient's studies, were either unremarkable or exhibited signs of meningeal irritation. CSF analysis exhibited elevated protein and pleocytosis; however, only one published case had similar elevations in CSF white blood cell and protein to the degree seen in this patient [8].

The exact pathophysiology of checkpoint inhibitor-associated encephalitis remains unclear. Proposed mechanisms include creating an exaggerated inflammatory response by increased T-cell activity against antigens that simultaneously exist in cancerous and healthy tissues (Fig. 3) [5]. Additionally, immunotherapeutic agents may cause increased levels of inflammatory cytokines and augmented complement-mediated inflammation through direct binding of antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA-4) expressed in normal tissue [1]. A recent cohort study of 290 patients who received atezolizumab demonstrated that the HLA-B27:05 genotype was over-represented in a subset of 7 patients who developed AIE, suggesting a possible genetic susceptibility [6].

Novel treatments, including atezolizumab, provide substantial hope for patients with cancer. However, as with all new therapies, increased use can lead to greater recognition of rare events. Given the growing use of immunotherapy and associated rare serious adverse events, it is crucial to understand the mechanisms underlying these adverse events and develop strategies to mitigate the risk.
| Patient (age, sex) | Indication | Duration of immunotherapy | Presentation | MRI | CSF | Citation |
|-------------------|------------|---------------------------|--------------|-----|-----|----------|
| 56 years, M       | NSCLC      | 17 days                   | Fever, altered consciousness expressive aphasia     | Normal | 20 WBC, 166 protein | Yamaguchi et al. [5] 2020 |
| 78 years, M       | NSCLC      | 13 days                   | Fever, altered consciousness                       | Normal | 139 WBC, 132 protein | Chang [6] 2020 |
| 72 years, F       | NSCLC      | 9 months                  | Gait disturbance, altered consciousness             | High signal in bilateral thalami | N/A | Nishijima et al. [7] 2021 |
| 53 years, F       | Squamous cell carcinoma of the cervix | 13 days | Confusion, headache, meningeal signs | Diffuse leptomeningeal enhancement | 553 WBC, >600 protein | Laserna et al. [8] 2018 |
| 38 years, F       | Breast cancer | 12 days | Seizures, somnolence | Diffuse hyperintense signal in the sulci | 15 WBC, 60 protein | Nader et al. [9] 2021 |
| 71 years, F       | NSCLC      | 14 days                   | Fever, altered consciousness                       | Normal | Normal WBC, 136 protein | Toyozawa et al. [10] 2020 |
| 55 years, M       | NSCLC      | 11 days                   | Fever, altered consciousness                       | Normal | Normal WBC, 130 protein | Toyozawa et al. [10] 2020 |
| 50 years, M       | NSCLC      | 11 days                   | Fever, altered consciousness                       | Enhancement along corpus collosum | 15 WBC, 358 protein | Toyozawa et al. [10] 2020 |

NSCLC, nonsmall cell lung cancer; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; WBC, white blood cell.
effects, clinicians must consider an expanded number of possible reasons for adverse events. Understanding the increased number of mechanisms will help clinicians recognize these effects in order to manage them expeditiously.

Acknowledgments

We would like to thank Dr. Ninad Desai and Judith Aquino for their help and arrangements.

Statement of Ethics

All personally identifiable information has been withheld and complete patient anonymity was guaranteed. Ethical approval is not required for this case report in accordance with local guidelines. Written informed consent was obtained from the patient’s next of kin for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There are no funding sources to report.

Author Contributions

Eiman Y. Ibrahim: conception and design. Eiman Y. Ibrahim, Weige Charlie Zhao, and Haritha Mopuru: collection and assembly of data. Eiman Y. Ibrahim, Weige Charlie Zhao, Haritha Mopuru, Christopher Janowiecki, and David J. Regelmann: article writing and final approval of article.
Data Availability Statement

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

References

1. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378(2):158–68.
2. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36(17):1714–68.
3. Singh V, Chu Y, Gupta V, Zhao CW. A tale of immune-related adverse events with sequential trials of checkpoint inhibitors in a patient with metastatic renal cell carcinoma. *Cureus*. 2020;12(6):e8395.
4. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389(10066):255–65.
5. Yamaguchi Y, Nagasawa H, Katagiri Y, Wada M. Atezolizumab-associated encephalitis in metastatic lung adenocarcinoma: a case report. *J Med Case Rep*. 2020;14(1):88.
6. Chang H, Shin YW, Keam B, Kim M, Im SA, Lee ST. HLA-B27 association of autoimmune encephalitis induced by PD-L1 inhibitor. *Ann Clin Transl Neurol*. 2020;7(11):2243–50.
7. Nishijima H, Suzuki C, Kon T, Nakamura T, Tanaka H, Sakamoto Y, et al. Bilateral thalamic lesions associated with atezolizumab-induced autoimmune encephalitis. *Neurology*. 2021;96(3):126–7.
8. Laserna A, Tummala S, Patel N, El Hamouda DEM, Gutiérrez C. Atezolizumab-related encephalitis in the intensive care unit: case report and review of the literature. *SAGE Open Med Case Rep*. 2018;6:2050313x18792422.
9. Nader R, Tannoury E, Rizk T, Ghaneh H. Atezolizumab-induced encephalitis in a patient with metastatic breast cancer: a case report and review of neurological adverse events associated with checkpoint inhibitors. *Autops Case Rep*. 2021;11(2):e2021261.
10. Toyozawa R, Haratake N, Toyokawa G, Matsubara T, Takamori S, Miura N, et al. Atezolizumab-induced aseptic meningitis in patients with NSCLC. *JTO Clin Res Rep*. 2020;1(1):100012.
11. Herbst RS, Giaccone G, de Marinis F, Reimnuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med*. 2020;383(14):1328–39.
12. Lukas R, Gandhi M, O’hear C, Hu S, Lai C, Patel J. Safety and efficacy analyses of atezolizumab in advanced non-small-cell lung cancer (NSCLC) patients with or without baseline brain metastases. *Ann Oncol*. 2017;28:ii28.