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

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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,

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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).

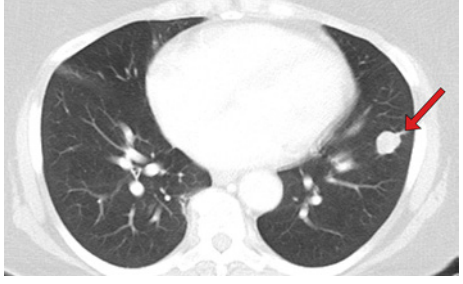

Fig. 1. Axial CT image of the chest demonstrating a 1.5 cm left lower lobe lung mass (red arrow).

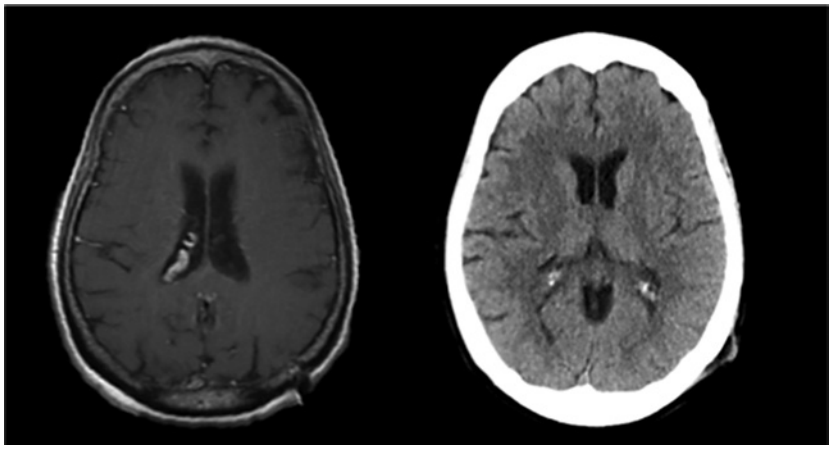

Fig. 2. (Left) Axial contrast-enhanced MRI of the brain and (right) axial noncontrast CT of the head showing no abnormality.

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

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Table 1. Selection of case reports and case series published on atezolizumab-associated encephalitis

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.

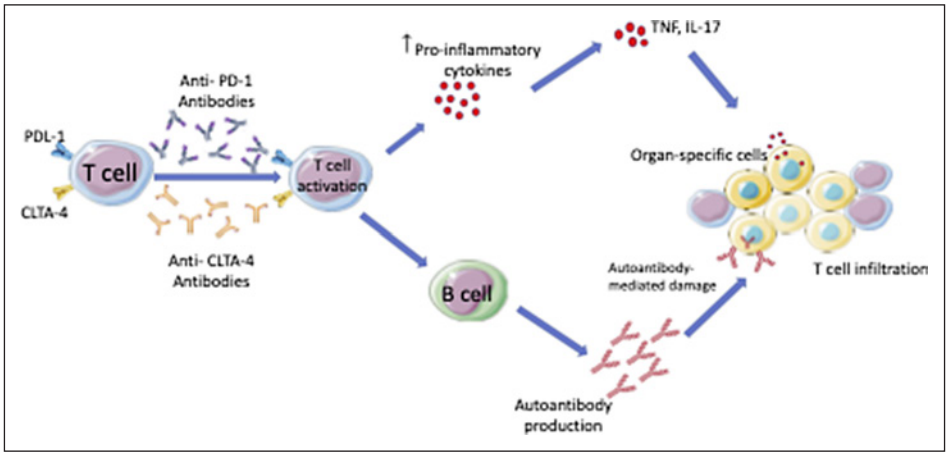

Fig. 3. Possible mechanism of immune-related adverse events due to immune checkpoint inhibitors.

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.

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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.

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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.

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