Atezolizumab-associated encephalitis in metastatic lung adenocarcinoma: a case report

Yoshitaka Yamaguchi 1*, Hikaru Nagasawa 1, Yuji Katagiri 2 and Manabu Wada 1

Abstract

Background: In recent years, immune checkpoint inhibitors have been widely used as a crucial therapy in malignant tumors. Immune checkpoint inhibitors can cause various autoimmune side effects called immune-related adverse events because they generate an exaggerated inflammatory response. Encephalitis associated with atezolizumab has rarely been reported as an immune-related adverse event. A case of encephalitis caused by treatment with atezolizumab is presented.

Case presentation: A 56-year-old Japanese man with lung cancer previously treated with surgery and chemotherapy was admitted with high fever, consciousness disorder, and motor aphasia. His first atezolizumab treatment was 17 days earlier. Admission brain magnetic resonance imaging with gadolinium enhancement showed no abnormalities. Cerebrospinal fluid showed cell count 20/l, protein 166 mg/dl, glucose 73 mg/dl, and interleukin 6 82.9 pg/ml (normal< 8.7 pg/ml). Atezolizumab-induced encephalitis was diagnosed. His symptoms improved the day after steroid pulse therapy was started. Following steroid pulse therapy, oral prednisolone 30 mg was started and tapered. The cerebrospinal fluid findings normalized on day 14. He was discharged on day 16 without neurological sequelae.

Conclusion: In this case of encephalitis associated with atezolizumab, prompt steroid pulse therapy led to a successful response, and the outcome was good. The cerebrospinal fluid level of interleukin 6 reflected the severity of the encephalitis well. Clinicians should be aware of the possibility of encephalitis after initiation of immune checkpoint inhibitors.

Keywords: Atezolizumab, Encephalitis, Immune checkpoint inhibitor, Immune-related adverse event, Lung adenocarcinoma, Programmed death ligand 1 inhibitor

Introduction

In recent years, immune checkpoint inhibitors have been widely used as a crucial therapy for patients with malignant tumors. Malignant cells prevent attacks from activated T cell-mediated immunity by inhibitory signals from programmed death ligand (PD-L) 1 and 2, which interact with programmed death (PD) 1 expressed on activated T cells. Immunotherapies targeting these ligands have shown efficacy and safety in the treatment of advanced malignant disease. Atezolizumab, an immune checkpoint inhibitor that targets PD-L 1 and 2 is approved for the treatment of urothelial carcinoma and non-small cell lung cancer and is currently under study for the treatment of gynecological, breast, lymphoma, melanoma, urological, and colorectal malignancies [1]. Immune checkpoint inhibitors can induce various autoimmune side effects called immune-related adverse events (irAEs) because they generate an exaggerated inflammatory response [2]. Neurological irAEs associated with immune checkpoint inhibitors include myasthenia gravis, Guillain-Barré syndrome, peripheral neuropathy, autonomic neuropathy, aseptic meningitis, encephalitis, and transverse myelitis [2]. However, encephalitis associated with atezolizumab has rarely been reported as an...
irAE. A case of encephalitis induced by treatment with atezolizumab is reported.

**Case presentation**

A 56-year-old Japanese man was admitted to our hospital because of high fever and consciousness disorder. He developed drowsiness and did not respond well to simple questions. He had been diagnosed with lung adenocarcinoma of the right lower lobe with upper right hilar lymph node metastasis (cT2N2M0). He was a taxi driver and had smoked until he was 55 years old (1 pack per day × 35 years). He had no other medical history or family history. He underwent right lobectomy 10 months prior to admission and had been treated with three courses of chemotherapy with a combination regimen of cisplatin plus vinorelbine, although positron emission tomography showed disease progression with multiple new metastatic lung lesions. Subsequently, he received three cycles of chemotherapy with a combination regimen of carboplatin plus nab-paclitaxel. He had received his first treatment with atezolizumab 17 days earlier for metastatic lung adenocarcinoma. His fever occurred about 1 week prior to admission. Neurological examination showed a consciousness disturbance (Glasgow Coma Scale E3V3M6) and motor aphasia. He did not show signs of pyramidal tract involvement, involuntary movement, ataxia, sensory disturbance, or autonomic disturbance. No other abnormal findings, including nuchal rigidity, were found.

Magnetic resonance imaging with gadolinium contrast of the brain on admission showed no abnormalities (Fig. 1). A cerebrospinal fluid (CSF) study demonstrated a cell count of 20/μl, protein of 166 mg/dl, and glucose of 73 mg/dl. The level of interleukin 6 (IL-6) in CSF was increased to 82.9 pg/ml (normal level < 8.7 pg/ml [3]). The CSF was negative for bacterial cultures and polymerase chain reaction for herpes simplex viruses 1 and 2 and cytomegalovirus. Serum antibody tests for paraneoplastic neurological syndrome including anti-Hu were...
negative. Thus, metastatic brain tumor, bacterial menin
gitis, herpes simplex encephalitis, and paraneoplastic
neurological syndrome were ruled out. Our patient was
diagnosed with encephalitis induced by atezolizumab,
and steroid pulse therapy with 1000 mg of methylpred
nisolone for 3 days was started on the second hospital
day. His symptoms including high fever, consciousness
disturbance, and motor aphasia improved immediately
the next day. After the steroid pulse therapy, oral admin
istration of prednisolone 30 mg (0.5 mg/kg) was started
and tapered. The CSF findings, except for mild pleocyto
sis (12/μl), were normalized on day 8. The value of IL-6
was decreased to 2.3 pg/ml. Oral administration of pred
nisolone ended on day 13. A subsequent CSF study on
day 14 showed an almost normalized cell count (7/μl)
and a normalized value of IL-6 (3.9 pg/ml) (Fig. 2). He
was discharged on day 16 without neurological sequelae.
After discharge, he was treated with combination
chemotherapy with a regimen of docetaxel plus ramucir
umab for lung adenocarcinoma without relapses of
encephalitis.

Discussion
A case of encephalitis that occurred after treatment with
atezolizumab was presented. Prompt diagnosis and initi
ation of steroid pulse therapy were successful. Long
term oral administration of prednisolone was not re
quired. The CSF level of IL-6 reflected the severity of
the encephalitis well.

Encephalitis associated with atezolizumab has rarely
been reported as an irAE; to the best of our knowledge,
only three cases have been reported [4–6]. Encephalitis
was not reported as an irAE for atezolizumab in Phases
1 and 2 of the POPLAR trial (atezolizumab vs. docetaxel
for patients with previously treated non-small cell lung
cancer). On the other hand, in the OAK trial, a random
ized, phase III study (atezolizumab vs. docetaxel in pa
tients with previously treated non-small cell lung
cancer), 5 of 609 patients (0.8%) treated with atezolizu
mab developed encephalitis [7]. Additionally, in the
Impower 150 study, a randomized, phase III study (ate
zolizumab in combination with carboplatin plus pacli
taxel with or without bevacizumab vs. carboplatin plus
paclitaxel and bevacizumab), 1 of 373 patients (0.3%) de
veloped encephalitis [8]. These patients developed
encephalitis about 2 weeks after treatment with atezoli
zumab and showed fever and consciousness disorder,
except for one who had a normal temperature [5]. CSF
pleocytosis and elevated protein levels are common.
Leptomeningeal enhancement or lesions of the brain
parenchyma on brain magnetic resonance imaging were
observed, except that two showed no abnormal findings,
as in the present case. Although the management of en
cephalitis associated with atezolizumab has not been
well-established, responses to steroid therapy were good,
and further additional treatment was not required [6].
On the other hand, in some cases of encephalitis associ
ated with nivolumab, a PD-1 inhibitor, additional treat
ment with immunoglobulin, or plasmapheresis was
required [9, 10].

The precise pathophysiology of irAEs remains uncer
tain. Some potential mechanisms include increased T-
cell activity against antigens that are present in tumors
and healthy tissue, increased levels of pre-existing

![Fig. 2 Clinical course of the present case. CSF cerebrospinal fluid; IL-6 interleukin 6; mPSL methylprednisolone; PSL prednisolone](image-url)
autoantibodies, increased levels of inflammatory cytokines, and enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue [1]. In the present case, the level of IL-6 in CSF was elevated in the acute phase and normalized after steroid therapy. To the best of our knowledge, this is the first case of encephalitis due to immune checkpoint inhibitors in which the level of IL-6 in the CSF was measured. Because IL-6 in the CSF is a representative cytokine reflecting inflammation in the central nervous system [3], excessive production of inflammatory cytokines was likely the cause for developing encephalitis in the present case. Increased autoantibodies may also be a possible mechanism, since one case report of encephalitis associated with nivolumab had N-methyl-D-aspartate receptor antibodies [9], but specific autoantibodies for developing encephalitis were not found in the present case.

In conclusion, a case of encephalitis associated with atezolizumab was presented. Prompt steroid pulse therapy led to a successful response, and the outcome was good. The CSF level of IL-6 reflected the severity of the encephalitis well. Clinicians should be aware of the possibility of encephalitis after initiation of immune checkpoint inhibitors. Because case reports of encephalitis associated with immune checkpoint inhibitors are very few, further investigation will be required to establish effective treatments for such life-threatening irAEs.

Abbreviations
CSF: Cerebrospinal fluid; CTLA-4: Cytotoxic T-lymphocyte antigen 4; IL-6: Interleukin 6; irAE: Immune-related adverse event; PD: Programmed death; PD-L: Programmed death ligand

Acknowledgements
The authors would like to thank FORTE Science Communications (https://www.fortescience.com/) for editing a draft of this manuscript.

Authors’ contributions
YY drafted the manuscript, accrued all data, and obtained the patient’s informed consent. HN, MW, and YK performed clinical supervision and provided clinical advice. All authors participated in writing the final manuscript. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written, informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
Not applicable.

Author details
1 Department of Neurology, Yamagata Prefectural Central Hospital, 1800 Aoyagi, Yamagata 990-2292, Japan. 2 Department of Respiratory Medicine, Yamagata Prefectural Central Hospital, 1800 Aoyagi, Yamagata 990-2292, Japan.

Received: 5 March 2020 Accepted: 25 May 2020
Published online: 04 July 2020

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, Laczetti 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. Kleinie TO, Zwerenez P, Zofiel P, Shiratori K. New and old diagnostic markers of meningitis in cerebrospinal fluid (CSF). Brain Res Bull. 2003;61(3):287–97.
4. Levine JJ, Somer RA, Hosoya H, Squillante C. Atezolizumab-induced encephalitis in metastatic bladder cancer: a case report and review of the literature. Clin Genitourin Cancer. 2017;5(5):e847–9.
5. Lasema A, Tumma S, Patel N, El Hamouda DEM, Gutierrez C. Atezolizumab-related encephalitis in the intensive care unit: case report and review of the literature. SAGE Open Med Case Rep. 2018;6:2050313X18792422.
6. Arakawa M, Yamazaki M, Toda Y, Saito R, Ozawa A, Kosaihira S, Kimura K. Atezolizumab-induced encephalitis in metastatic lung cancer: a case report and literature review. eNeurologicalSci. 2018;14:49–50.
7. 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.
8. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288–301.
9. Williams TJ, Benavides DR, Patrice KA, Dalmaz JO, de Ávila AL, Le DT, et al. Association of autoimmune encephalitis with combined immune checkpoint inhibitor treatment for metastatic cancer. JAMA Neurol. 2016;73(8):928–33.
10. Burke M, Hardesty M, Downs W. A case of severe encephalitis while on PD-1 immunotherapy for recurrent clear cell ovarian cancer. Gynecol Oncol Rep. 2018;24:51–3.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.