



## Letter to the Editor

## Atezolizumab-induced encephalitis in metastatic lung cancer: a case report and literature review



## ARTICLE INFO

## Keywords:

Atezolizumab  
Encephalitis  
irAE

## Dear Editors:

Atezolizumab is an available programmed death ligand 1 (PD-L1) inhibitor approved by the Food and Drug Administration for the treatment of non-small cell lung cancer. Although immune checkpoint inhibitors are antitumorigenic, they have the potential to cause immune-related adverse events (irAEs), including but not limited to dermatological, gastrointestinal, hepatic, endocrine, and other less common inflammatory events including neurologic events. The incidence of irAEs remains particularly low in the central nervous system (CNS). Here, however, we present a case of irAEs in the CNS that are directly attributable to the use of atezolizumab.

A 78-year-old man was referred to our hospital with complaints of confusion and fever. He had received his first dose of atezolizumab 13 days ago for recurrent metastatic lung cancer. The patient was diagnosed with a metastatic lung tumor of the left temporal lobe in January 2014. He underwent a left temporal lobectomy and positron emission tomography, which revealed lung adenocarcinoma with the upper right hilar lymph nodes positive (stage cT1cN1M1b). The patient underwent chemotherapy and radiation therapy to treat the cancer. However, in May 2018, the tumor had still progressed, and a standard treatment of atezolizumab 1200 mg per day was started intravenously. A neurological examination revealed somnolence and nuchal rigidity, with no other abnormal findings. Administration of methylprednisolone 1000 mg per day, empiric antibiotics (ceftriaxone), and acyclovir was also started intravenously.

Initial brain magnetic resonance imaging (MRI) with gadolinium on day 3 showed no abnormal findings other than the left temporal lobectomy. On day 1, cerebrospinal fluid (CSF) analysis demonstrated a normal glucose level, cell count of 6/ $\mu$ L, protein concentration of 106 mg/dL, myelin basic protein concentration of 115.3 pg/mL, and negative cytological findings. The CSF sample was negative for bacterial cultures, and serological analysis of potential virus contamination (for herpes simplex virus 1 and 2 polymerase chain reaction, Varicella Zoster virus antibodies, Cytomegalovirus antibodies, Epstein-Barr Virus antibodies) also yielded negative results. Serological paraneoplastic autoantibodies [AMPH, CV2, PNMA2, Ri, Yo, Hu, recoverin, SOX1, titin, zic4, Tr(DNER), GAD65] were negative. Other paraneoplastic antibodies (antibodies against the voltage-gated potassium channel complex and *N*-methyl-D-aspartate receptors) were also negative.

On day 2, CSF analysis demonstrated a high cell count of 139/ $\mu$ L

and protein concentration of 132 mg/dL. However, on day 5, the patient's clinical and neurological status had improved to the point that he was able to follow basic commands. After initial treatment with methylprednisolone 1000 mg for 5 days, the patient was transitioned to prednisolone 1 mg/day/kg with the goal of slowly being tapered off over 8 weeks. On day 22, CSF analysis revealed remarkably positive changes (cell count: 3/ $\mu$ L, protein concentration: 51 mg/dL). At his last neurological examination before discharge on day 58, the patient was well-oriented and able to sit down and communicate.

The immune checkpoint suppresses the activation of immune cells by maintaining an inhibitory signal and helps to maintain self-tolerance [1]. Cancer cells are able to escape detection and thus survive by manipulating the immune system, including regulatory immune cells [2]. The programmed cell death protein 1 (PD-1)/PD-L1 pathway is one of these immune checkpoints. Atezolizumab and immune checkpoint inhibitor, and anti-PD-L1 antibody, are assumed to be antitumorigenic by blocking PD-1/PD-L1 signaling, thus releasing the inhibition of effector T cells.

Immune checkpoint inhibitors can have autoimmune side effects called irAEs. To date, several published clinical trials have documented the occurrence of irAEs, including neurological side effects. However, irAEs of the CNS, such as encephalitis, have rarely been reported as an AE. A phase I study of atezolizumab and a phase II study, the POPLAR trial (atezolizumab vs. docetaxel for patients with previously treated non-small cell lung cancer), did not report any case of irAEs of the CNS. However, the OAK trial, a randomized phase III study comparing atezolizumab to docetaxel in patients with previously treated non-small cell lung cancer, reported 4 cases of encephalitis [3]. In these 4 cases, encephalitis developed within approximately 2 weeks of atezolizumab administration. In all cases, initial symptoms predominantly included consciousness disorders, and CSF analysis showed high levels of cell and protein concentrations. Abnormal brain MRI findings of diffuse leptomeningeal enhancement or lesions of brain parenchyma were observed in 3 of the 4 cases. Two other cases have been reported since the commercial release of atezolizumab. One of these cases consists of atezolizumab-induced encephalitis in metastatic bladder cancer [4], while the other consists of a cervical squamous cell carcinoma [5]. In both cases, CSF analysis revealed high levels of cell and protein concentrations. Viral antibodies and paraneoplastic autoantibodies quantified by serological and CSF analysis yielded negative results. Corticosteroids were used as the initial immunological treatment in each

<https://doi.org/10.1016/j.ensci.2018.12.001>

Received 22 November 2018; Accepted 16 December 2018

Available online 17 December 2018

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case. In cases of atezolizumab-induced encephalitis, corticosteroid treatment alone improved the symptoms and no additional immunological treatment was required. In some cases of encephalitis induced by nivolumab as used as a PD-1 inhibitor, corticosteroid treatment was followed by immunoglobulin or plasma exchange [6,7]. In our case, improvements in clinical symptoms and laboratory values were observed following treatment with corticosteroids.

Atezolizumab is indicated for non-small cell lung cancer and will very likely be applied to other malignant tumors. Very few cases of atezolizumab-related encephalitis have been reported to date. The present case of encephalitis attributable to atezolizumab was successfully treated with the prompt use of high-dose steroids. It will be necessary to develop effective treatments for such life-threatening AEs.

### Conflicts of interest

The authors declare no financial or other conflicts of interest.

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