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Letter to the Editor

Nivolumab treatment followed by atezolizumab induced encephalitis and neuropathy with antiganglioside antibodies

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Dear Editor

1. Background

Immune checkpoint inhibitors (ICIs) have been widely used to treat various refractory cancers and have improved overall survival in recent years. The targets of current ICI therapies and the corresponding drugs are cytoplasmic T lymphocyte-associated antigen-4 (CTLA-4: ipilimumab), programmed death-1 (PD-1: pembrolizumab, nivolumab, and cemiplimab), and programmed death ligand-1 (PD-L1: atezolizumab, durvalumab, and avelumab) [1,2]. While ICIs enhance antitumor immune responses, several immune-related adverse events (irAEs) can be caused by breaking self-tolerance. We report a case of immune-related encephalitis and neuropathy with antibodies against ganglioside after sequential treatment with nivolumab and atezolizumab.

2. Case report

A 48-year-old man was diagnosed with metastatic lung adenocarcinoma (stage cT4N3M1$_a$). He participated in a double-blind, randomized phase III study to check the efficacy and safety of nivolumab in combination with carboplatin, paclitaxel, and bevacizumab. He was treated with the study medication for 7 months, and belonged to the nivolumab treatment group (360 mg every 3 weeks: first, in combination with carboplatin, paclitaxel, and bevacizumab for 3 months, and then with bevacizumab for 4 months). His primary lung lesion was temporarily reduced, but new metastatic lung lesions progressed afterwards. As second line chemotherapy (docetaxel hydrate + ramucirumab) for 4 months was not effective, treatment with atezolizumab (1200 mg every 3 weeks) as third line chemotherapy was started. Sixteen days after the first administration of atezolizumab (day 1), the patient was admitted to our institution with a 3-day history of fever, headache, and vomiting. Although fluids and empiric antibiotics were started after hospitalization, his state of consciousness deteriorated into stupor and he fell into convulsions on day 2. Brain magnetic resonance imaging (MRI) showed T2 fluid-attenuated inversion recovery (FLAIR) hyperintensities in the bilateral mesial temporal lobe (Fig. 1A). Cerebrospinal fluid (CSF) showed inflammatory findings (leukocytes: 12/μl, neutrophils: 19%, proteins: 162 mg/dl, glucose: 50 mg/dl, no malignant cells). The CSF culture was negative for bacteria and fungi. Herpes simplex virus DNA in the CSF was also negative, as assessed by PCR. Serum paraneoplastic antibodies [AMPH, CV2, PNMA2, Ri, Yo, Hu, recoverin, SOX1, titin, zic4, Tr (DNER), GAD65] were negative. We diagnosed the patient's illness as autoimmune encephalitis induced by ICIs. Atezolizumab therapy was discontinued, and he was treated with high-dose intravenous methylprednisolone (1000 mg/day: 3 days) from day 4. Although his state of consciousness gradually improved after methylprednisolone administration, he developed visual loss (from day 6), painful numbness of all limbs, clumsiness of his fingers, and gait unsteadiness (from day 9). On day 10, neurological examination showed a defect in the central visual field in both eyes, areflexia of the legs, mild muscle weakness in all limbs, and severe dysesthesia of the limbs in a stocking-and-glove distribution, however his state of consciousness was completely recovered. Ophthalmologists diagnosed his visual impairment as retinal phlebitis. Nerve conduction studies (NCS) showed slightly low amplitudes of both compound muscle action potentials and sensory nerve action potentials in the upper and lower limbs (Fig. 1B). The NCS results suggested that the patient suffered from acute axonal sensorimotor polyneuropathy. Serum antiganglioside antibodies were positive (anti-GM1 IgG: mildly positive, and anti-GalNAc-GD1a IgG: strongly positive). Notably, an antecedent infection was not present. As the second course of high-dose intravenous methylprednisolone from day 11 followed by oral prednisolone (35 mg/day) did not improve the patient's symptoms, intravenous immunoglobulin (IVIg; 400 mg/kg/day) was also given over 5 days from day 17. Within several days, his pain in the limbs, finger clumsiness, and gait unsteadiness improved. The paresthesia also reduced, although not completely. On day 21, the FLAIR hyperintensity signals were slightly resolved in the follow-up brain MRI (Fig. 1C). On day 27, the patient left our hospital, taking oral prednisolone (20 mg/day). The dose of prednisolone was gradually tapered. On day 92, the follow-up NCS showed an improvement in the decreased

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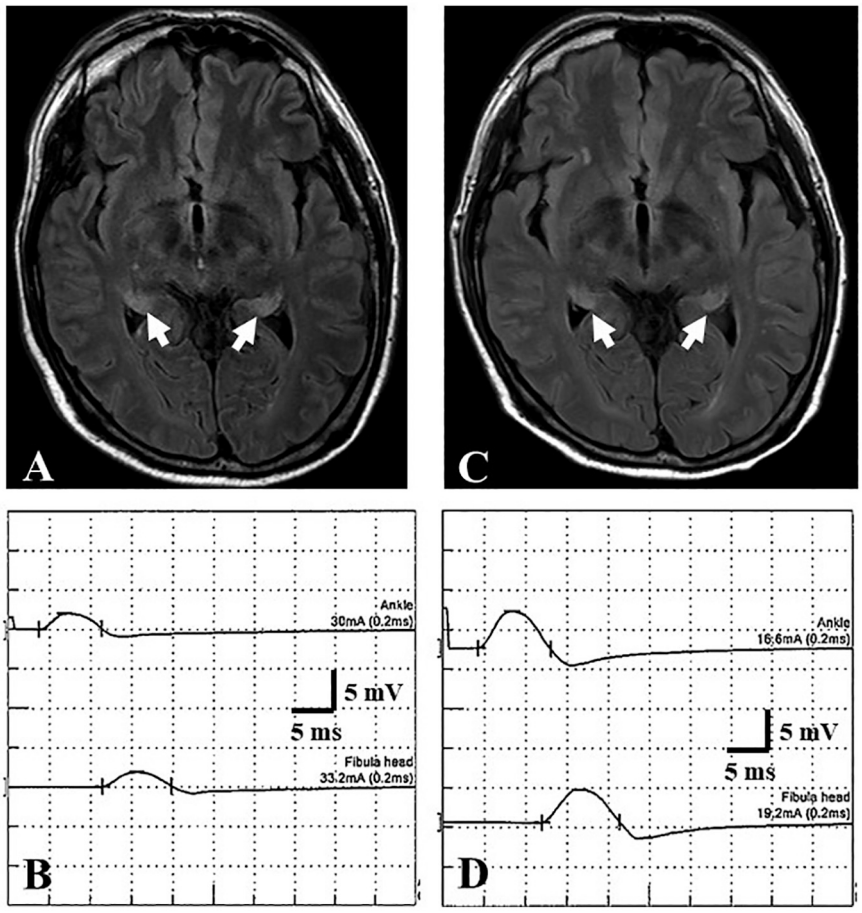

Fig. 1. Head MRI (A, C) and nerve conduction studies (B, D).
Head magnetic resonance imaging (MRI) on day 3 showed T2 fluid-attenuated inversion recovery (FLAIR) hyperintensities in the bilateral mesial temporal lobe (A, white arrows). Nerve conduction study (NCS) on day 10 showed slightly low amplitudes of compound muscle action potentials (CMAP) in the right peroneal nerve (B, ankle: 2.0 mV and fibula head 1.9 mV). After performing immunotherapy, the FLAIR hyperintensity signals in the head MRI were slightly resolved on day 21 (C, white arrows), and NCS on day 92 showed an improvement in the decreased amplitudes of CMAP in the right peroneal nerve (D, ankle: 4.7 mV and fibula head 4.2 mV).

amplitudes of both compound muscle action potentials and sensory nerve action potentials (Fig. 1D). On day 110, the serum anti-GalNAc-GD1a IgG antibodies remained strongly positive, but anti-GM1 IgG antibodies were not detected. Although his paresthesia of the limbs remained, he could return to work.

3. Discussion

Neurological irAEs are not very frequent, occurring in 1%–3% of ICI-treated patients [2]. One study reported that 18% of patients with neurological irAEs were impaired in both the central and peripheral nervous systems [1]. In our case, encephalitis occurred 16 days after the initial treatment with atezolizumab. Although the nivolumab treatment ended 5 months earlier, we could not exclude the possibility that the patient's neurological complications were affected by nivolumab. In fact, a previous study reported that nivolumab-bound T cells were detected more than 20 weeks after a final infusion [3]. Hence, we should be cautious about the risk of irAEs when sequentially treating with another ICI.

Neurological irAEs with antiganglioside antibodies are rare [2,4]. To our knowledge, there has been only one case report [5]. Fukumoto et al. reported a case of nivolumab-induced acute demyelinating neuropathy with antiganglioside antibodies (GM2 IgM and GalNAc-GD1a IgM). In their case, the symptoms of neuropathy worsened in spite of prednisolone administration, but improved after IVIg treatment. While the encephalitis in our case improved soon after administration of methylprednisolone, the neuropathy in our case was also resistant to steroid therapy and improved after IVIg treatment. Although we could not exclude the possibility that steroid therapy also gradually showed the effect against neuropathy, IVIg might be more effective against neurological irAEs with antiganglioside antibodies.

Declaration of Competing Interest

None.

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