

Case Report

Multiple Cranial Neuropathies Similar to Orbital Apex Syndrome Associated with Pembrolizumab: A Case Report

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Keywords

Orbital apex syndrome · Pembrolizumab · Immune-related adverse events · Non-small-cell lung cancer · Cranial neuropathies

Abstract

Neurotoxicity is one of the more serious immune-related adverse events (irAEs) linked to immune checkpoint inhibitors and calls for prompt diagnosis and treatment. We describe a case of posttreatment anti-programmed death-1 immune checkpoint inhibitor pembrolizumab-induced oculomotor, optic, and trigeminal neuropathy in an 84-year-old female patient with recurrent pulmonary adenocarcinoma. After she received 13 cycles of pembrolizumab, she experienced hyponatremia, anorexia, and right ptosis. There were signs of the suspected irAEs of pembrolizumab, including trigeminal neuropathy, optic neuropathy, and oculomotor neuropathy. Steroid pulse therapy had good results for her neurological findings. We reported this case despite reports of pembrolizumab-induced mononeuropathy of the oculomotor and optic nerves because multiple cranial neuropathies like orbital apex syndrome are thought to be uncommon.

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Introduction

Immune checkpoint inhibitors (ICIs) are widely used in the treatment of lung cancer. Programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1) in particular has shown effectiveness and safety in the immunotherapy of cancers including primary lung cancer [1]. PD-1/PD-L1 inhibitors have also been demonstrated to be superior to conventional chemotherapy, both monotherapy and in combination, in several cancer types. In recent years, there have been numerous studies on the advantages of combining ICIs with other anticancer agents such as tyrosine kinase inhibitors and cytotoxic agents. Studies have also utilized PD-L1 expression in tumor cells as a predictor of response to ICIs therapy [2–4]. The first-line treatment for postoperative recurrent and metastatic non-small-cell lung cancer with strong PD-L1 expression is pembrolizumab monotherapy, a fully humanized IgG4 monoclonal antibody against PD-1 [5]. In contrast, as the use of ICIs increases, we are seeing a greater number of immune-related adverse events (irAEs) in clinical settings that were not present when using earlier cytotoxic anticancer agents. Among the diverse irAEs of ICIs, neurotoxicity is infrequent and rarely experienced. In this article, we discuss our encounter with multiple cranial neuropathies, a particularly uncommon adverse event that resembles orbital apex syndrome.

Case Presentation

The patient, an 84-year-old nonsmoker with no significant medical history, underwent treatment. She underwent robotic-assisted thoracoscopic right upper lobectomy for primary pulmonary adenocarcinoma p-T2N0M1a, stage IVA, high PD-L1 expression, and TPS >50%. Right pleural dissemination was visible on the postoperative CT at 1 month. The patient was referred to our division and was given 200 mg of pembrolizumab every 3 weeks as monotherapy. She had anorexia and right ptosis following 13 cycles of therapy. Sodium, ACTH, and cortisol levels were 124 mEq/L, 4.4 pg/mL, and 0.3 µg/mL, respectively, suggesting hypopituitarism with hyponatremia. A neurological examination revealed decreased right visual acuity (index valve) and decreased right ocular motor function (impaired supraduction, infraduction, and adduction). In addition, the right eye was abducted during midline vision, and complete ptosis of the right eyelid was observed. Right trigeminal neuropathy and decreased sensation in the right nasal cavity were also noted. On contrast-enhanced T1-weighted images of the right optic nerve, orbital contrast-enhanced MRI (Fig. 1a) revealed an abnormal enhancing effect on the entire length of the right optic nerve on contrast-enhanced T1-weighted images. Additionally, optic nerve sheath edema was seen, as well as a high-signal area inside the right optic nerve that was mildly enlarged on contrast-enhanced T2-weighted images (Fig. 1b). Visual evoked potentials testing showed prolonged P100 latency in the right eye. The test for repetitive nerve stimulation came back normal. The cerebrospinal fluid examination also showed no abnormalities. There were no signs of autoantibodies like those against the thyroid, anti-acetylcholine receptor, or muscle-specific tyrosin kinase (MuSK). Based on these findings, a diagnosis of right optic neuritis was made.

Every week, for a total of 3 times, methylprednisolone 1,000 mg was given over 3 days. The dose of corticosteroid was gradually tapered from prednisolone to 30 mg/day. Her right eye's visual acuity improved following the first dose of steroid pulse therapy. After the second steroid pulse therapy was completed, her right eye movement improved. The right optic nerve's swelling improved, the T2-weighted image signal inside the optic nerve decreased, and the enhancing effect of the optic nerve sheath vanished on contrast-enhanced

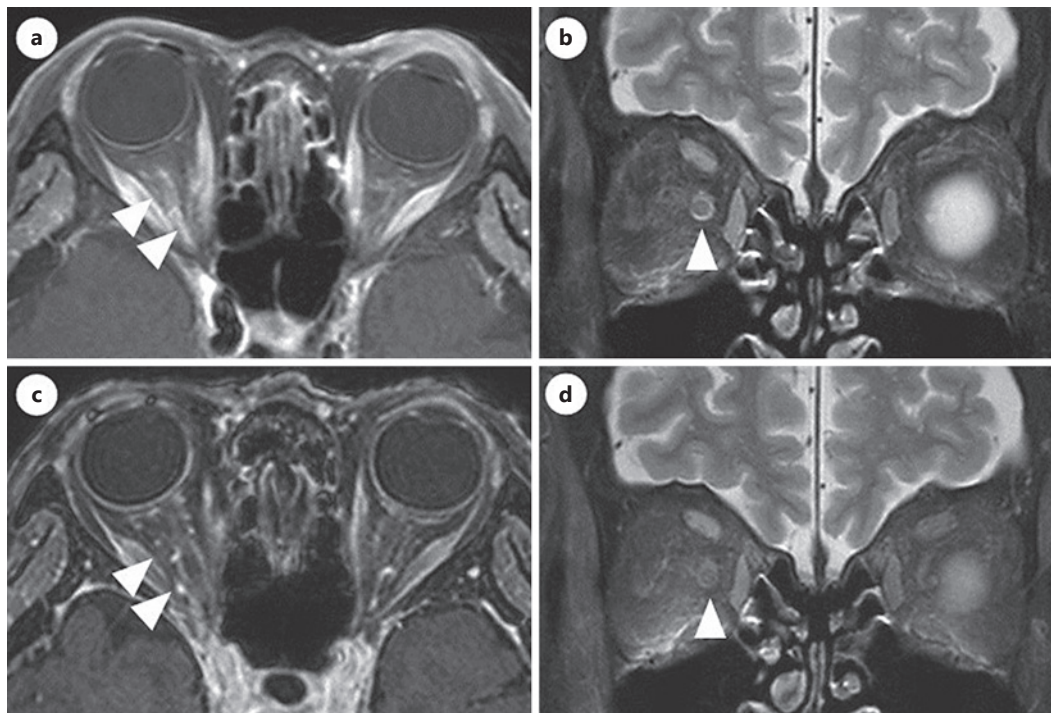


Fig. 1. **a** Contrast-enhanced head MRI T1-weighted image (T1WI) before the start of treatment showed an abnormal enhancement effect on the entire length of the right optic nerve. **b** Contrast-enhanced head MRI T2-weighted image (T2WI) before the start of treatment showed T2WI high signal inside the right optic nerve, mild swelling of the optic nerve, and optic nerve sheath edema. **c** Contrast-enhanced head MRI T1WI performed after steroid pulse treatment showed improvement of abnormal enhancement effect of the right optic nerve. **d** Contrast-enhanced head MRI T2WI performed after steroid pulse treatment showed improvement of enlargement of the right optic nerve, T2WI high signal inside the optic nerve, and enhancement effect of the optic nerve sheath.

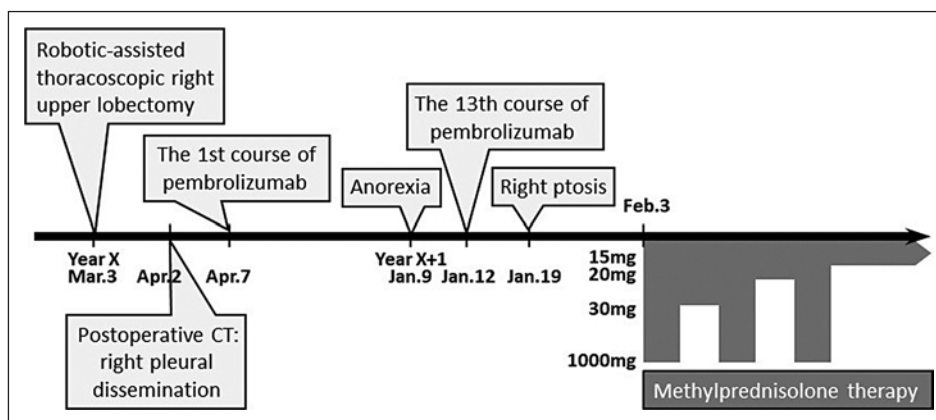


Fig. 2. Clinical course from diagnosis of lung cancer to treatment of neuritis. Right ptosis appeared 7 days after the 13th course of pembrolizumab administration.

orbital MRI imaging after the second steroid pulse therapy (Fig. 1c, d). And her nasal hypesthesia also improved after the treatment. Figure 2 depicts a timeline for this case presentation.

Discussion

Here, we present a rare instance of neurological deficits associated with pembrolizumab monotherapy that were reminiscent of orbital apex syndrome. Orbital apex syndrome is a disorder caused by damage to the optic nerve (II), oculomotor nerve (III), trochlear nerve (IV), abducens nerve (VI), and the ophthalmic branch of the trigeminal nerve (V1) [6]. The superior rectus, external rectus, inferior rectus, and internal rectus muscles, as well as the optic nerve duct, through which the optic nerve and ophthalmic artery pass internally, are all located in the orbital apex, which is also home to the annulus of Zinn, a tendinous structure [7]. The superior orbital fissure is traversed by the oculomotor nerve, the trochlear nerve, the abducens nerve, and the ophthalmic branch of the trigeminal nerve. The optic canal, the oculomotor nerve, the nasociliary nerve (a branch of the ophthalmic branch of the trigeminal nerve), and the abducens nerve also pass medial to the annulus of Zinn and are nearby. Orbital apex syndrome is a set of symptoms that result from a disease affecting these structures that pass through the optic canal and superior orbital fissure [7].

Ophthalmoplegia and visual loss are the most typical early clinical manifestations of OAS, and these symptoms can be brought on by inflammatory, infectious, neoplastic, iatrogenic/traumatic, and vascular causes [6]. From an anatomical distance, OAS is similar to the superior orbital fissure syndrome and the cavernous sinus syndrome, but OAS differs from the others in that the optic nerve is involved [7]. A head MRI revealed findings that were suggestive of optic neuritis, and the patient was brought to our hospital with complaints of ptosis, diminished visual acuity, and restricted eye movement. These were symptoms observed in OAS. It is well known that systemic inflammatory diseases or generalized orbital inflammations are the primary cause of OAS [7]. In our case, pembrolizumab may produce nerve inflammations, leading to OAS-like symptoms.

The frequency of irAE in first-line pembrolizumab monotherapy for non-small-cell lung cancer with PD-L1 expression $\geq 50\%$ is 32.9% [8]. PD-1 inhibitors are known to cause neurotoxicity, which can manifest as tremors, visual disturbance, dysarthria, ataxia, paralysis, paresthesia, and convulsions. Peripheral neuropathy, optic neuritis, myasthenia gravis, and Guillain-Barre syndrome have also been reported [9]. As for adverse effects on the cranial nerves, there are reports of oculomotor neuritis with pembrolizumab and abducens nerve and facial nerve palsy with nivolumab [10].

For treatment of cranial neuropathy due to side effects of ICIs, observation, prednisone 0.5–1 mg/kg, and gabapentin/pregabalin/duloxetine are recommended in case of pain [11]. In 2 cases, systemic steroids were used to treat nivolumab-induced abducens and facial nerve palsy and oculomotor neuropathy, respectively [10]. In this case, there was damage to the optic nerve, oculomotor nerve, and trigeminal nerve. Since there was no pain, we decided to treat the patient with steroids (three courses of corticosteroid pulses plus oral prednisone at 0.5 mg/kg to begin and taper off). This helped the patient's ptosis, eye movement, and nasal sensory disturbance, and it also improved her visual acuity.

There may be some possible limitations in this study. Even though this patient had multiple cranial neuropathies, there is still no proof that pembrolizumab caused these neuropathies. Although this case is considered to be a rare case with no other reports, the number of cases of irAEs may be small because pembrolizumab and other ICIs are relatively new drugs, and further accumulation of irAEs is needed. The therapeutic effects and side effects of ICIs are a field of active research and discussion at this time. The mechanism and symptoms of cranial nerve disorder caused by irAEs will be clarified by additional research in the future, and this study may be helpful in this regard.

Due to the irAE of pembrolizumab, we saw a case of ophthalmoplegia, optic nerve abnormality, and trigeminal neuropathy. Pembrolizumab has been linked to reports of

mononeuropathy of the ophthalmic and optic nerves [12, 13], but instances of multiple cranial neuropathies similar to OAS are thought to be uncommon. If a patient is taking an ICI, it is important to take irAEs into account when examining them if they have decreased visual acuity, ptosis, or abnormal eye movements.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Taku Nishimura was a major contributor in writing the manuscript. Toshio Sakatani, Shunichi Matsuda, Toshihiro Yoshizawa, and Kazuhiro Usui reviewed and edited the manuscript. Toshio Sakatani, Hideyuki Takeshima, Shunichi Matsuda, Toshihiro Yoshizawa, and Kazuhiro Usui contributed to the patient management.

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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