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Case Report

Third Cranial Nerve Palsy after Monoclonal Antibody Therapy for Lung Cancer: A Case Report

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Keywords
Cancer · Cranial nerve · Lung · Metastasis · Pembrolizumab · Side effects

Abstract
Immune checkpoint inhibitors (ICIs) have shown promise in treating cancer patients, and pembrolizumab is a monoclonal IgG4 antibody that targets a human cell surface protein (receptor) called PD-1. Among the side effects, a rare cranial nerve palsy unrelated to the surgical treatment may occur. We report a case of a woman, which after neurosurgical treatment for cerebellar metastasis presented painless third cranial nerve palsy. The benefits of ICIs have been ascertained, but side effects also take place. Neurological symptoms should be recognized early to avoid substantial morbidity, and if necessary, the oncologic treatment should be changed.

Introduction

Immune checkpoint inhibitors (ICIs) have well-known neurological adverse effects. The incidence of adverse effects is 3.8% with anti-CTLA4 antibodies, 6.1% with anti-PD1 antibodies, and 12.0% with the combination of both [1]. The clinical spectrum of neurological

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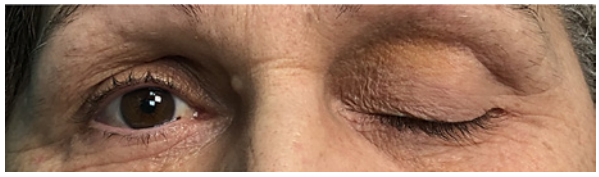

Fig. 1. Patient with complete left blepharoptosis 1 week after the first dose of pembrolizumab.

involvement is heterogeneous. The most frequently reported adverse neurological effects are cephalalgia, encephalopathy, meningo-radiculoneuritis, acute inflammatory neuropathy, and myasthenic syndrome. Among the peripheral nervous system adverse events, the myasthenic syndrome has been reported as the most common PD-1 inhibitor-associated neuromuscular complication [2]. Although rare, cranial nerve involvement (i.e., VII and VIII cranial nerves) has also been reported [3–6]. Even more rare is painless third cranial nerve palsy [4, 6, 7].

Case Description

A 59-year-old woman with a smoking habit underwent a left cerebellar convexity metastasis resection. Postoperative magnetic resonance imaging (MRI) revealed complete macroscopic metastasis removal, and a total-body computed tomography scan showed the primary lung tumor. After the resection, histology showed an adenocarcinoma that expressed TTF-1, napsin A, and CK7.

Eight weeks after the cerebellar metastasis removal, the patient started immunotherapy with pembrolizumab. However, 1 week after the first dose, she complained of painless, progressive, left eyelid ptosis, which was unresponsive to the ice-pack test (Fig. 1). A prompt neurological assessment disclosed signs of complete palsy in the left third cranial nerve (hypo and exotropia and mydriasis). A follow-up contrast MRI revealed the absence of vascular lesions on DWI, T2* imaging and FLAIR, a metastasis recurrence in the same cerebellar location, but no lesion in the left oculomotor nucleus or third cranial nerve and no orbital abnormality (Fig. 2a–c). A neurophysiological evaluation of the neuromuscular junction at the cranial and limb sites showed normal results, as did electroneurography in the upper and lower limbs. No serum anti-Ach receptor or anti-GQ1b antibodies were found. Dexamethasone was started at 4 mg qid, and another resection of the recurring lesion was performed; this was followed by cerebellar radiation therapy. Another cycle of immunotherapy with pembrolizumab was recommended, but the patient did not consent, due to fear of contralateral eyelid ptosis. A course of another chemotherapeutic agent was proposed, but the primary disease showed further progression, which prevented starting the new cycle. The third cranial nerve palsy remained unchanged for 3 months after its appearance.

Discussion

The present case is of interest, because the presenting symptom (i.e., ptosis) is not specific, and it broadens the differential diagnosis to include myasthenia gravis, Miller-Fisher syndrome, ocular myositis, cavernous sinus thrombophlebitis, etc. A thorough neuroimaging evaluation with negative results can easily rule out the latter two diagnoses, and the absence of anti-GQ1b antibodies renders the Miller-Fisher syndrome unlikely, as well as possible brainstem dysfunction manifesting with oculomotor abnormalities due to GAD65

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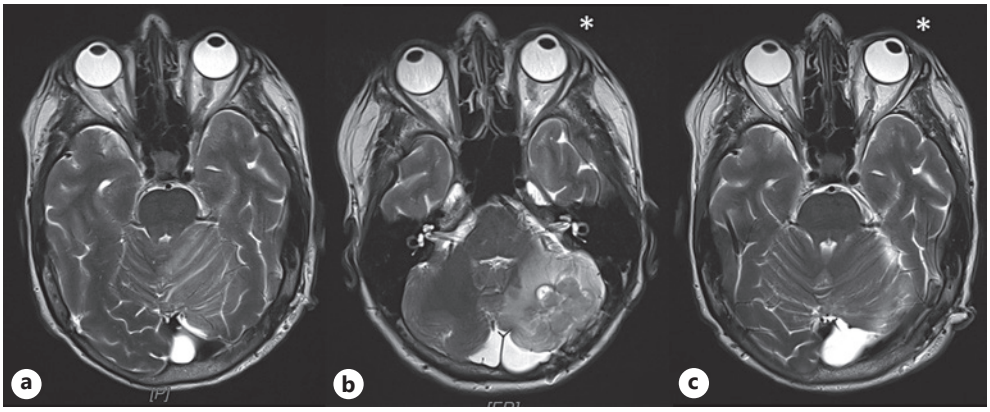

Fig. 2. T2-weighted MRIs of the patient. **a** Normal eyes' alignment after removal of left cerebellar metastasis. **b** Patient complaining diplopia and recurrent left cerebellar metastasis before second surgical treatment (80 days after first surgical resection). The image shows eyes' misalignment due to left III cranial nerve palsy (asterisk), the recurrent left cerebellar metastasis but no other pathological tissue or mesencephalic alterations. **c** After second surgical treatment (100 days after first surgical resection), eyes' misalignment and left III cranial nerve palsy persist.

neurological autoimmunity. In patients with antibodies targeting GAD65, the brainstem dysfunction never occurs in isolation [8]; rather, it accompanies at least one of the core manifestations (stiff person spectrum disorders, cerebellar ataxia, and epilepsy with or without limbic encephalitis). Since our patient manifested no hypertonia, ataxia, or seizures, we considered a diagnosis of GAD65 neurological autoimmunity unlikely.

On the other hand, patients with ICI-induced myasthenia gravis can present with the presence or absence of anti-Ach receptor antibodies, but a negative ice-pack test, with a concomitant ocular deviation and mydriasis, made the clinical diagnosis straightforward. Our observation reinforces the notion that, in patients treated surgically for brain metastasis, isolated cranial nerve lesions that are anatomically unrelated to the surgical field, but emerge during immunotherapy, must be regarded as adverse events. An MRI should be performed to confirm this diagnosis, to ascertain a possible tumor recurrence, and to exclude secondary causes. As observed in the patient described here, ICI-related cranial nerve impairment has a major impact on the primary disease, because it may impair the patient's ability to consent to a first-choice cancer treatment.

Conclusion

The benefits of pembrolizumab have been ascertained, but side effects also take place. In particular, previously absent neurological symptoms unrelated to surgery might appear. These symptoms should be recognized early to avoid substantial morbidity, and if necessary, the oncologic treatment should be changed.

Statement of Ethics

The Policlinico "Umberto I" Ethics Committee granted an exemption from requiring ethics approval since this is a case report. Written informed consent for the publication of this report and face photo was obtained from the patient.

Conflict of Interest Statement

The authors declare that they have no competing interest.

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Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Paolo Missori, Angela Ambrosone, and Leonardo Cristofani. The first draft of the manuscript was written by Paolo Missori, Francesco Fattapposta, and Antonio Currà. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Data are available on request due to privacy/ethical restrictions. Inquiries can be directed to the corresponding author.

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