CASE REPORT

Isolated Abducens Nerve Palsy Following Pembrolizumab

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ABSTRACT

Pembrolizumab is a checkpoint inhibitor targeting the programmed cell death 1 receptor of lymphocytes and is used in the treatment of solid tumours including melanoma. The authors report a 64-year-old man treated with pembrolizumab for stage IV cutaneous melanoma (primary cutaneous melanoma of the right lower back) with liver metastases. The patient developed a horizontal binocular diplopia due to an isolated unilateral cranial nerve VI palsy. Following 1 week of high dose oral steroid therapy and cessation of the drug, the patient's nerve palsy and associated diplopic symptoms improved dramatically, and after 6 weeks of oral steroid taper and drug cessation, the palsy resolved completely. Few reports of checkpoint inhibitor autoimmune-induced isolated cranial nerve palsies have been described, and this is the first report of drug-induced isolated cranial nerve VI palsy.

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Introduction

The introduction of checkpoint inhibitor therapy has revolutionized the landscape of treatment options for systemic cancers. However, as these treatments are increasingly utilized, systemic sequelae due to autoimmune effects of these medications are correspondingly noted.¹ Pembrolizumab and nivolumab specifically block the programmed cell death-1 (PD-1) receptor upregulated on exhausted T lymphocytes and other immune cells. Ipilimumab inhibits cytotoxic T lymphocyte antigen-4 (CTLA-4), which leads to cytotoxic T lymphocyte activation and depletes regulatory T cells. In doing so, tumour cells are unable to evade immune surveillance mechanisms and durable objective responses can be achieved in multiple histologies, such as melanoma. However, at the same time, the body's natural ability to immune regulate is suppressed.² Severe systemic immune-related adverse effects (irAEs) due to PD-1 blockade with nivolumab or pembrolizumab have been reported to occur in approximately 10% of patients,³ and rates of irAEs are significantly higher with combined nivolumab plus ipilimumab.⁴ Neurological, including ocular, toxicity has been reported to a much smaller degree in checkpoint inhibitor treated patients: a 1.67% rate in >4800 patients was reported in the largest cohort to

date.⁵ Here, we describe a case of an isolated autoimmune-induced cranial nerve VI palsy due to pembrolizumab.

Case report

A 64-year-old man with metastatic cutaneous melanoma (primary cutaneous melanoma of the right lower back) to the liver was treated with intravenous nivolumab 1 mg/kg plus ipilimumab 3 mg/kg for 2 doses with an early partial response. He was then continued on PD-1 maintenance with pembrolizumab (2 mg/kg administered by intermittent infusion piggyback every 3 weeks) with continued disease stability. Adverse events during the first year of therapy included mild fatigue, arthralgias, hypothyroidism requiring levothyroxine, and vitiligo. The patient also has a past medical history significant for well-documented, well-controlled hypertension and coronary artery disease. After 13 months of therapy, he was referred to the ophthalmology clinic with acute onset binocular horizontal diplopia, worse on right lateral gaze. Ocular exam was significant only for right lateral rectus palsy with 25 prism diopters of esotropia (ET) in primary gaze. All other cranial nerves were intact and no other neurological

abnormalities were noted. Slit lamp exam revealed normal lids and conjunctiva, few scattered punctate corneal epithelial erosions in both eyes, deep and quiet anterior chamber, normal iris, mild nuclear sclerotic cataracts, and absence of vitreous inflammation in both eyes. Fundus exam was normal in both eyes with normal optic nerve and retina exams. Laboratory findings showed only a decreased thyroid stimulating hormone (0.5 mIU/L) with intact free T4 (1.14 ng/dL). MRI of the brain was performed with and without gadolinium contrast which showed no evidence of brain metastases, leptomeningeal disease, perineural invasion (PNI), acute abnormality nor infarction. There was no atrophy or enhancement of the lateral rectus muscle, and no entrapment of the medial rectus muscle. The patient was started on oral prednisone 1 mg/kg/day dosing and discharged home. Further pembrolizumab infusions were held. He was re-evaluated in the clinic 1 week later and found to have improved to 18 prism diopters ET. Oral corticosteroid treatment was continued using a slow gradual taper. One week later, he had improved to 12 prism diopters ET, and after 6 weeks his lateral rectus palsy was resolved from initial presentation and symptoms of diplopia in all directions of gaze had resolved. The decision was made to continue to hold pembrolizumab and to follow the patient closely with repeat imaging, with a plan to consider further therapy only upon evidence of tumour regrowth. The patient has now been followed for 7 months following his initial diagnosis of cranial nerve VI palsy and has remained off pembrolizumab with no evidence of tumour regrowth on imaging. He has had no recurrence of his cranial nerve palsy and no occurrence of other cranial nerve palsies during this time.

Discussion

This patient's rapid and complete recovery of his large angle abducens nerve palsy following treatment with systemic corticosteroid strongly suggests an autoimmune aetiology of his isolated cranial nerve VI palsy. To our knowledge, this is the first report of an *isolated* cranial nerve VI palsy as an immune-related ocular side effect. Cranial nerve III palsy ($n = 1$), cranial nerve VII palsy ($n = 1$), and combined cranial nerve VI and VII palsy ($n = 1$) have been described previously, all with complete resolution following systemic

corticosteroid initiation and checkpoint inhibitor cessation.⁶ This case is also unique in that onset of neurotoxicity occurred after 13 months of treatment, while in the vast majority (75%) of reported cases, patients experience the onset of neurotoxicity within the first 4 months of treatment.⁷

While unlikely, the authors cannot definitively rule out PNI or perineural spread (PNS) of melanoma to the abducens nerve. PNS is rarely associated with melanoma and more commonly associated with other cancers of the skin such as squamous cell carcinoma, adenoid cystic carcinoma, and lymphoma, among others.⁸ Additionally, without any evidence of melanoma metastases to the head and neck, it would be very rare for first and new metastases to appear as PNS to cranial nerve VI. PNS most commonly occurs along branches of the trigeminal nerve, or the facial nerve in cases of metastases to the parotid gland.^{8,9} Once the tumour spreads via the perineural route to a more central location, such as the cavernous sinus, other cranial nerves are oftentimes involved, but to our knowledge there are no case reports to date of isolated PNS to the abducens nerve.¹⁰ In the absence of symptoms such as pain, burning sensation, or paresthesias, which have been reported to be present in up to 60% of patients with PNS, PNS is less likely.⁸ MRI has been shown to have a detection rate in large nerve PNS of greater than 95%,¹¹ and in our patient, it showed no enlargement or enhancement of nerves or other findings suggestive of PNS. However, absence of MRI findings does not definitively rule out PNS. The patient has been followed closely for 7 months following his cranial nerve VI palsy while remaining off melanoma treatment and off additional steroid treatment and has experienced no recurrence of his cranial nerve palsy and no onset of new ocular or neurologic symptoms which is reassuring.

While also unlikely given this patient's rapid improvement immediately following stopping the checkpoint inhibitor and initiating oral steroid, the authors also cannot definitively rule out microvascular cranial nerve VI palsy, which accounts for up to 36% of isolated cranial nerve VI palsies.¹² The patient does have a history of coronary artery disease and hypertension; however, he has a well-documented history of excellent control of these medical co-morbidities and is without any prior incidence of microvascular insults prior to initiation of his checkpoint inhibitor treatment. In a large prospective review by Tamhankar

et al., more than 60% of patients with cranial nerve palsies due to non-microvascular causes also had vasculopathic risk factors.¹³ Importantly, our patient exhibited improvement in his nerve palsy as early as 1 week after starting oral steroids. While spontaneous improvement of microvascular cranial nerve VI palsies does occur in approximately 86% of patients,¹⁴ this improvement typically occurs gradually over a period of 8–24 weeks on average.¹⁵ In contrast, our patient showed rapid improvement from 25 to 18 PD of ET within 9 days of initiating oral prednisone, followed by improvement to 10 PD after a total of 15 days on oral prednisone taper. After 29 days, he had improved to only 6 PD of ET, and by his repeat exam date 43 days after initiation of the steroid taper, his cranial nerve VI palsy had resolved completely.

Pembrolizumab and the checkpoint inhibitors suppress immune tolerance to decrease tumour growth, and by concurrently suppressing the body's natural immune regulatory system can cause autoimmune sequelae. It has been hypothesized that subsequent microvascular inflammation and perineural oedema may contribute to the pathophysiology of cranial nerve palsy specifically.⁷ In all reported cases of checkpoint inhibitor-induced cranial nerve palsy, corticosteroid treatment in combination with drug cessation has resulted in complete resolution of the palsy.⁶

As immune checkpoint blockade becomes more ubiquitous across oncology and as prolonged patient survival allows for extended medication use, the importance of prompt diagnosis and management of immune-related toxicities induced by immune checkpoint blockade will grow. Efficacy data to date suggest patients with melanoma requiring interruption of checkpoint inhibition due to irAEs do not have worse efficacy outcomes, underscoring the importance of cessation of PD-1 blockade when serious irAEs arise.^{16,17} While neurotoxicity is reported to be present in a small cohort of patients, this case serves as another example that the toxicities can be significant. There is presently a paucity of data from which practitioners can draw to guide management, and as the use of these drugs expand, it will be important to continue to contribute to the existing database of cases to concurrently expand our knowledge of data and outcomes.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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