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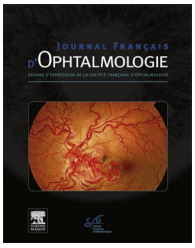

LETTER TO THE EDITOR

Permanent bilateral mydriasis after treatment with nivolumab/ipilimumab for cutaneous melanoma

Mydriase bilatérale permanente après traitement par nivolumab/ipilimumab pour mélanome cutané

Introduction

Immune checkpoint inhibitors, such as nivolumab and ipilimumab, are a new type of immunotherapy drug used for the treatment of advanced cutaneous melanoma and other tumors [1]. Due to their mechanism of action, they may induce immune-related adverse events (IRAE). Ocular side effects may present in different ways and have reported to occur in 1% to 6% of the treated patients [2].

We present the case of a patient suffering from stage IIIC cutaneous melanoma, which developed a permanent bilateral mydriasis as a possible IRAE after treatment with ipilimumab/nivolumab.

Case description

A 36-year-old woman diagnosed with stage IIIC cutaneous melanoma located in the back was treated by a margin ample excision and a lymphadenectomy. A complete body PET-CT scan ruled out metastasis. The patient was then included in a clinical trial evaluating the adjuvant treatment with nivolumab 40 mg versus nivolumab 240 mg and ipilimumab 1 mg/kg. Till today, the clinical trial is still ongoing and the treatment that the patient we report has not yet been undisclosed as the study is double blinded. After eleven cycles of treatment along five months, the patient had to suspend the treatment after developing toxic colitis that required hospitalization and steroid treatment. Two weeks after being discharged, the patient presented to our department referring asymptomatic bilateral mydriasis and assured that she had not taken any sympathomimetic and parasympathomimetic drugs. Near and far best corrected visual acuity was 20/20 in both eyes and the patient did not present accommodation insufficiency. Extraocular movements and convergence tests were normal. Both pupils were areflexic and mydriatic with a pupil size of 8 mm. Slit-lamp examination and fundus examination were normal. Mydriasis did not revert after pilocarpine 0.1% test nor after pilocarpine 2% test one hour after instillation (Fig. 1). Thyroid and adrenal hormone levels were normal. Drug urine test was negative for amphetamines, cocaine, cannabis, methamphetamine, opioids, benzodiazepines, tricyclic antidepressants, barbiturates, methylenedioxymethamphetamines and methadone. Brain MRI proved absence of brain metastasis nor any other lesions. Antineuronal antibodies were negative.

Follow-up at six, twelve and twenty-four months after the diagnosis of the IRAE, bilateral mydriasis was persistent, and pupils were still areflexic. The pilocarpine test was negative in all revisions, although there was a progressive reduction in pupil size compared to the first visit despite persistent mydriasis (Fig. 2). The rest of the ophthalmic examination was normal, and the patient remained asymptomatic. No other systemic side effects were noticed.

Discussion

Bilateral mydriasis may occur in different scenarios. For instance, in systemic diseases such as Miller-Fisher syndrome, botulism, paraneoplastic syndrome, drug administration and midbrain lesions [3]. However, in these cases, mydriasis is accompanied by ophthalmic or systemic signs or symptoms. In paraneoplastic syndromes and autonomous dysfunction, mydriasis is due to a tonic pupil hence being hypersensitive to pilocarpine [4]. In midbrain lesions, mydriasis may be accompanied by vertical supranuclear gaze palsy, internuclear ophthalmoplegia, convergence insufficiency, among others [5].

These disorders are unlikely in our patient given the findings upon examination and the absence of other signs and symptoms throughout two years of follow-up, and given the fact that the complementary tests were normal. Repeated use of parasympathomimetic substances would affect accommodation, and sympathomimetic substances would revert with pilocarpine [6].

Nivolumab and ipilimumab, alone or in combination, are monoclonal antibodies approved for the treatment of metastatic melanoma [7]. Nivolumab acts as blocking programmed cell death protein 1 (PD-1) [7]. Ipilimumab acts as a blocking signal of CTLA-4 antigen, stimulating the activation of cytotoxic T cells [8]. Both drugs belong to the group of immune checkpoint inhibitors and are increasingly being more used for the treatment of melanoma and other cancers. They may develop IRAE as they enhance the antitumoral response of one's immune system and the antigens of the tumor may be expressed in other tissues [2,9]. Some of the ophthalmic IRAE reported are uveitis, optic neuropathy, orbital inflammation, dysthyroid-like orbitopathy, myasthenia-like disorder, giant cell arteritis and vasculitis, serous retinal detachment, dry eye, ulcerative keratitis, and episcleritis [1,9]. Mydriasis is an unusual adverse event of

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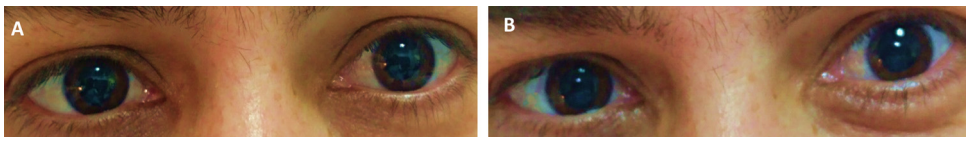

Figure 1. First visit. A. Prior to pilocarpine 2% instillation. B. 60 minutes after instillation with pilocarpine 2%.

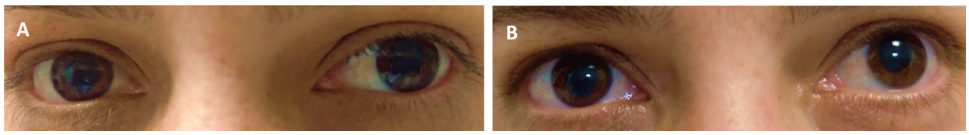

Figure 2. Persistent mydriasis, though observing a discreet reduction in pupillary size. A. One year after the first visit. B. Two years after the first visit.

these drugs and only two published case reports are available in the literature, to the best of our knowledge [2,10]. In both the reported cases, the pupil reacted to pilocarpine unlike our case. On the other hand, in the case described by Wu et al. [10], the patient developed Guillain-Barré syndrome associated with a right tonic pupil after the first dose of ipilimumab 10 mg/kg. After treatment, the patient recovered a normal pupil function, although other autonomic dysfunction symptoms were persistent. In the case reported by Rodríguez et al. [2], bilateral mydriasis was observed in a patient that was enrolled in a clinical trial evaluating the treatment of cutaneous melanoma with ipilimumab and a vaccine against melanoma. One day after treatment, the patient developed bilateral serous retinal detachments, nausea, vomiting and fatigue. After discontinuing the treatment and steroid therapy, subretinal fluid resolved although mydriasis was persistent after a year of follow-up with scarce improvement in pupillary diameter size (from 9 mm to 7 mm in the right eye and 8 mm in the left eye) [2].

Melanoma affected cells express certain proteins in the melanocytes, such as gp100, MART-1 and tyrosinase [6,9]. The recognition of antigen peptides derived from these proteins by the T-cells may potentially develop an autoimmune response against tissues that are rich in these proteins, such as the iris.

Given that other causes were ruled out and considering that the treatment of cutaneous melanoma and the occurrence of bilateral mydriasis were aligned in time, it may be reasonable to consider bilateral mydriasis as a possible IRAE of nivolumab or combined therapy of ipilimumab and nivolumab. The fact that our patient received a higher dosage than the two available reported cases, and the presence of iris pigmentation could be a sign of the damage of the iris sphincter receptors. Moreover, normal accommodation, persistent mydriasis after two years and no reaction to pilocarpine, rules out a parasympathetic damage.

No similar symptoms have been reported with nivolumab, although it is yet to be clarified whether the patient was in the combined treatment arm of nivolumab and ipilimumab.

Conclusion

We consider that permanent bilateral mydriasis may be a dose-dependent immune-related adverse event of nivolumab and ipilimumab immunotherapy.

Disclosure of interest

The authors declare that they have no competing interest.

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