SHORT COMMUNICATION

TITLE:

Immune privilege: failure of immunotherapy in controlling metastatic cutaneous melanoma to the eye

RUNNING TITLE:

Ocular immune privilege in immunotherapy

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ABSTRACT:

This report concerns a 49-year-old female with cutaneous malignant melanoma and systemic metastases. These resolved following combination immunotherapy with ipilimumab and nivolumab. She subsequently experienced unilateral floaters, an increase in iris pigmentation and pigmentary glaucoma. The eye progressively lost vision and became painful due to iris neovascularisation. The clinical diagnosis was of cutaneous melanoma metastatic to the vitreous, ciliary body and iris. Enucleation was performed for symptom control, with histopathology confirming the clinical diagnosis. The immune privilege of the eye may preclude ocular metastasis control with immunotherapy. Ocular symptoms in such patients merit referral to an ophthalmologist.

KEYWORDS:

Metastatic cutaneous melanoma, melanoma, ocular metastasis, immunotherapy, immune privilege

INTRODUCTION:

The eye is known to be a site of immune privilege, where immune responses are controlled and sometimes inhibited. Immune privilege in the eye is the result of a complex array anatomical, physiological and immunoregulatory mechanisms that prevent the induction and expression of many immune responses.[1] We describe a rare case of metastatic cutaneous melanoma which responded well to immunotherapy, but subsequently presented with metastatic deposits to the eye.

CASE:

A 49-year-old white female was referred to the Ocular Oncology Clinic with iris heterochromia and right ocular hypertension refractory to medical and surgical therapy. Seven months prior, she first presented with visual symptoms of floaters, haloes, seeing “rainbows” and decreased right eye vision, with a raised right intraocular pressure (52 mmHg). Past ocular history included right Posner-Schlossman syndrome, a type of uveitis associated with recurrent raised intraocular pressure, so her initial presentation was considered to be a further attack, perhaps precipitated by immunotherapy. She was treated with topical and oral intraocular pressure lowering medications.

Medical history was remarkable for two cutaneous melanomas excised from the right groin (0.93mm Breslow thickness) 6 years previously and right upper arm (1.7mm Breslow thickness) 4 years previously. Two months before her ocular symptoms, she was diagnosed with cutaneous melanoma metastatic to the right parotid gland, right

groin lymph nodes, subcutaneously in the left temple and chest, and multiple areas in the brain. Biopsy of the superficial lesions revealed metastatic cutaneous melanoma with BRAF mutation and NRAS wild type. She was started on combination immunotherapy shortly after diagnosis, with ipilimumab and nivolumab. She developed significant side effects after 2 cycles of immunotherapy which included rash, colitis, hepatitis, hypokalaemia, deranged liver enzymes and iritis involving both eyes, treated with systemic and topical steroids. The third cycle of immunotherapy was abandoned due to the side effects. She underwent a follow-up positron emission tomography computed tomography (PET CT) and magnetic resonance imaging (MRI) of the brain 6 months after initiation of immunotherapy, and this showed an excellent partial response to treatment systemically and in the brain. MRI/PET CT at 9 months post treatment showed a complete metabolic response systemically and a sustained partial response in the brain.

Her raised right intraocular pressure was refractory to maximal medical therapy and remained elevated even after a trabeculectomy, undertaken elsewhere. As there was increasing iris heterochromia, she was referred to our service. On examination, her best corrected visual acuities were 6/18 in the right eye and 6/5 in the left eye. There was a right relative afferent pupillary defect (RAPD) and iris heterochromia (brown iris in the right eye and blue (her natural colour) in the left) (Fig. 1a & 1b). Slit lamp examination of the right eye revealed speckled pigmentation on an iris that was thickened throughout (Fig. 1a), a flat trabeculectomy bleb with pigmentation at the sclerostomy site (Fig. 1c), clumps of pigment in anterior chamber inferiorly and on the

corneal endothelium (Fig. 1a), and seclusio pupillae. Gonioscopy of the right anterior chamber angle revealed 360˚ of synechial closure. There was no iris neovascularisation and no iritis. In the vitreous of the right eye, there were further clumps of pigment visible (Fig. 1d). No discrete mass was seen in the right fundus. The intraocular pressure was 50 mmHg in the right eye and 12 mmHg in the left eye. Ultrasound B-scan of the right eye revealed iris bombe, a cluster of cells at 6 o'clock on the iris, dense vitreous opacities, some of which were clustered, and no discrete mass lesion in the eye or in the bleb.

The clinical diagnosis of metastatic cutaneous melanoma to the right eye was made. Two weeks later, she developed worsening pain in her right eye, iris neovascularisation and a hyphaema. Due to pain and increasing tumour invasion, her right eye was enucleated.

Microscopic examination of the globe revealed a sizeable population of lightly and moderately pigmented epithelioid cells distributed within both the anterior and posterior segments (Fig. 2). These coated the posterior cornea, anterior iris, angle, ciliary processes and retina, as well as floating freely within the vitreous (Fig. 2). Immunohistochemistry was positive for MelanA and HMB45, consistent with melanoma. Within the vitreous was a separate population of CD68-positive cells consistent with melanophages (Fig. 2d). Melanoma cells infiltrated the iris stroma, but there was no infiltration of the ciliary body, retina or choroid (Fig. 2c & d). Additionally, below the trabeculectomy bleb, pigmented cells were present. These were positive for

CD68 immunohistochemistry rather than MelanA, supporting the cells in this area being melanophages rather than melanoma cells (Fig. 2b). Features of glaucoma were also present, including ganglion cell loss.

DISCUSSION:

The eye is a rare site of distant metastases from cutaneous melanoma and accounts for less than 5% of all metastases to the eye and orbit.[2] Intraocular metastases from melanoma are generally observed in patients with disseminated metastases, who frequently also present with central nervous system involvement.[3] For cutaneous melanomas that metastasise to the eye, the choroid is the most commonly involved site (where they can mimic a primary uveal melanoma), followed by the vitreous, conjunctiva, retina and the anterior segment.[2]

The prognosis for metastatic cutaneous melanoma has historically been poor, with a low 5-year survival rates and median overall survival of less than 1 year.[4] Recent development of immune checkpoint inhibitors has revolutionised the treatment of metastatic melanoma with vastly improved survival rates. Dual checkpoint blockade with concurrent ipilimumab and nivolumab now shows 3-year overall survival rates of up to 58.3%.[5,6]

Although checkpoint inhibitors have demonstrated efficacy in the treatment of brain metastases[7-9], there have been no reports regarding efficacy towards intraocular metastases. Our report illustrates a case of metastatic cutaneous melanoma that

responded well to immunotherapy with dual checkpoint inhibitors, but had intraocular metastases which failed to respond.

As far as we are aware, there is only 1 other report in the literature of metastatic cutaneous melanoma to the eye that presented after immunotherapy.[10] Kanavati et al.[10] reported a case of a 63-year-old woman who presented with floaters and a descending curtain across her right vision, 1 year after diagnosis of metastatic malignant melanoma and 7 months after receiving her last dose of Ipilimumab. That case had bilateral vitreoretinal involvement as non-pigmented globular vitreous opacities and pale retinal lesions, treated with bilateral vitrectomy and external beam radiotherapy to both eyes with good results.[10] In contrast, our case had unilateral infiltration, of the vitreous and anterior chamber with raised intraocular pressure, so vitrectomy and radiotherapy were not suitable.

Features of our case and that reported by Kanavati et al., highlight the property of the eye as an immunoprivileged site. Immune privilege in the eye consists of anatomical, physiological and immunoregulatory processes that restrict the induction and expression of both the innate and adaptive immune responses.[1] Anatomical features include the blood-ocular barrier that restricts entry of macromolecules and inflammatory cells into the eye, reduced expression of MHC class I and II molecules, expression of MHC class 1b molecules, and the relative avascular nature of many structures in the eye.[1] Physiological processes include multiple cell membrane-bound molecules such as CRPs, FasL, TRAIL and PD-L1 that inhibit cells of the innate

and adaptive immune responses.[1] The aqueous humour of the eye is also filled with multiple soluble immunosuppressive and anti-inflammatory factors which include the TGF-β, α-MSH, VIP, and CGRP.[1]

Various therapeutic protocols for metastatic cutaneous melanoma to the eye have been described with mixed results.[2,3] Most common forms of treatment involve radiotherapy, resections of the ocular tumours, enucleation, evisceration or observation.[2] Other treatments that have been described include vitrectomy, subconjunctival chemotherapy, direct confluent laser photocoagulation and cryotherapy.[2] Early treatment is associated with a more favourable outcome, whereas uncontrolled progression often leads to irreducible neovascular glaucoma leaving enucleation as the only option.[3] Chemotherapy has been used to treat intraocular metastasis of melanoma but with poor outcomes, and it is therefore not recommended.[2,11]

In summary, this report illustrates a rare case of metastatic cutaneous melanoma to the eye that presented after an excellent systemic response to immunotherapy. This is presumed to be due to ocular immune privilege and the mode of action of immunotherapy that activates T cells, rather than acting directly on the tumour. Physicians need to be mindful of patients with metastatic cutaneous melanoma treated with immunotherapy, who subsequently present with new visual symptoms.

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FIGURE LEGENDS:

Figure 1: (a & b) Slitlamp photographs showing iris heterochromia. (a) Speckled pigmentation on the right iris that is thickened throughout and clumps of pigment in the inferior anterior chamber. (b) Normal left eye colour. (c) Pigmentation underneath a flat conjunctival bleb at previous trabeculectomy site. (d) Ultra-widefield fundus photograph of the right eye showing hazy view to the fundus with clumps of pigmented “floaters” in the vitreous.

Figure 2: (a) Photomicrograph of anterior segment showing lightly pigmented melanoma cells coating iris (yellow arrow), lens and ciliary processes. (H&E stain, x1 objective). (b) There are pigmented cells subconjunctivally (yellow arrow) and within the sclera at the trabeculectomy site. These are positive for CD68 and negative for MelanA (not shown), indicating melanophages rather than melanoma cells. (H&E stain, x4 objective). (c) Melanoma cells infiltrate the iris stroma, angle and trabecular meshwork (yellow arrow), and coat the ciliary processes. (H&E stain, x10 objective). (d) There are MelanA positive cells in the vitreous (yellow arrow) but sparing the retina, indicating vitreous involvement by melanoma. There are also MelanA negative cells which are positive for CD68 (not shown) indicating melanophages. (MelanA immunohistochemistry, x4 objective)