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Case Report

Bilateral Vitiligo-Like Depigmentation of Choroid and Retinal Pigment Epithelium Associated with Ipilimumab-Nivolumab Therapy for Metastatic Cutaneous Melanoma

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Melanoma · Oncology · Systemic therapy · Choroidal vitiligo · Checkpoint inhibitors

Abstract
Introduction: Ipilimumab and nivolumab are checkpoint inhibitors that are known to cause a multitude of inflammatory ocular adverse events. Here we report a patient with poliosis and symptomatic depigmentation of the choroid and retinal pigment epithelium (RPE) associated with checkpoint inhibitor therapy for cutaneous melanoma. ***Case Presentation:*** The patient presented with floaters in both eyes and concerns for intraocular metastases of metastatic cutaneous melanoma after 1 month of therapy with ipilimumab and nivolumab. External examination revealed poliosis of her eyebrows and eyelashes. Fundus photography demonstrated multiple 1–3 disc-diameter hypopigmented placoid flat areas in the RPE/choroid exposing underlying choroidal vessels in both eyes. At subsequent evaluation 7 months later (after an additional 6 months of checkpoint inhibitor therapy), the lesions appeared more blanched. Evaluation nearly 20 months after the initial presentation showed no significant changes from her prior visit despite cessation of checkpoint inhibitor therapy for 13 months. ***Conclusion:*** Checkpoint inhibitor therapy for cutaneous melanoma metastases can cause depigmentation of the choroid and RPE that must be differentiated from progression of intraocular melanoma.

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Introduction

Novel immunotherapy agents have revolutionized the treatment of many cancers, especially malignant melanoma. Numerous studies have shown that immunotherapy agents, whether prescribed as monotherapy or in combination, significantly reduce the risk of death and progression of disease among various different tumor subtypes [1, 2]. Ipilimumab and nivolumab (Ipi/Nivo) are examples of two different types of checkpoint inhibitors. Ipi/Nivo work synergistically to enhance host T-cell defenses by inhibiting cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 (PD1), respectively, and are used as first-line therapy for metastatic melanoma [3, 4]. Many types of inflammatory ocular adverse events have been reported with Ipi/Nivo combination therapy, including uveitis, retinal inflammation, retinal vasculitis, and Vogt-Koyanagi-Harada-like syndrome [5]. Furthermore, choroidal involvement with checkpoint inhibitor-related toxicity can present with birdshot chorioretinopathy, choroidal thinning, and choroidal effusions [5]. Herein, we report a novel finding of vitiligo-like loss of pigmentation in the retinal pigment epithelium (RPE) and choroid in a patient with multi-metastatic cutaneous melanoma being treated with ipilimumab and nivolumab. The CARE Checklist has been completed by the authors for this case report and is attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535745).

Case Report

A 47-year-old woman with metastatic cutaneous melanoma treated with Ipi/Nivo was referred to ocular oncology clinic for evaluation of multifocal bilateral choroidal lesions concerning for possible choroidal metastasis. She was diagnosed with cutaneous melanoma 6 years prior with metastatic disease to the brain and abdomen discovered 4 years later. On presentation to our clinic, she reported symptomatic floaters while concurrently receiving treatments of nivolumab. Her presenting visual acuity was 20/20 and 20/25, and intraocular pressures were 13 and 11. External examination revealed poliosis of her eyebrows and eyelashes (Fig. 1). Fundus photography was notable for multiple 1–3 disc-diameter flat hypopigmented/amelanotic placoid areas exposing underlying choroidal vessels in both eyes (Fig. 2a, b). OCT through the lesions demonstrated choroidal hyporeflectivity without retinal elevation (Fig. 2c–f). No other attributable cause for her floaters was found on exam. Treatment-related depigmentation of uveal tissues was suspected. The patient continued Ipi/Nivo therapy for six more months but subsequently stopped therapy due to severe acute pancreatitis and autoimmune hypophysitis. Fundoscopic examination 1 month after stopping therapy demonstrated further depigmentation/blanching of the previously identified hypopigmented areas in both eyes. There was no evidence of enlargement or development of new areas of involvement (Fig. 2g, h). Fluorescein angiography showed early window defects through the affected areas with normal perfusion and no evidence of vasculitis (Fig. 2i–l).

At her most recent ophthalmologic examination, nearly 20 months after initial presentation, the patient had remained off all therapy for 13 months and stated her floaters were unchanged OU. The choroidal lesions were unchanged from her most recent visit but remained more blanched than her original exam (Fig. 2m, n). In speaking with the patient nearly 3 years after her initial encounter, her vision is stable, and her floaters remain unchanged OU.

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Fig. 1. Poliosis of eyebrows and eyelashes seen with Ipi/Nivo therapy.

Discussion

Novel immunotherapies have significantly improved clinical outcomes in numerous types of cancers, but these therapies are also associated with systemic adverse effects that must be closely monitored. Development of systemic vitiligo/poliosis after starting checkpoint inhibitors, such as Ipi/Nivo, has been associated with robust anti-melanoma immunity and predicts improvement in survival [6]. Our patient's history of autoimmune hypophysitis is consistent with an immune-mediated reaction involving the central nervous system. However, given that there were no signs of clinical or angiographic optic nerve involvement or overt inflammatory reaction in the eye, even shortly after the onset of hypophysitis, our patient's choroidal findings are unlikely to be part of a central nervous system generalized autoimmune reaction. Instead, these findings appear to be a more targeted form of immunity affecting pigmented cells. This cross-reactivity between uveal and cutaneous melanocytes appears to play a role in cases of cutaneous vitiligo seen after treatment of uveal melanoma [6]. While it is possible that the presence of such effect may indicate good therapeutic response, the prognostic value or mechanism underlying these findings is not clearly established. Fortunately, these lesions did not significantly affect the patient's visual acuity and her vision remained stable, even in extended follow-up nearly 3 years after initial presentation. Continued follow-up is needed to assess any further, longer-term impacts – if any – of these lesions on visual acuity.

Rarely, amelanotic metastatic infiltration of the choroid can produce similar-sized lesions. This process was unlikely in our patient as the depigmented areas remained unchanged over 13 months after cessation of therapy, and exhibited no evidence of subretinal fluid or growth, as would be seen with metastasis. Lack of retinal elevation further makes choroidal metastases less likely.

Other processes can present with hypopigmented choroidal lesions and should be considered when differentiating more complex ocular manifestations. For example, varicella zoster has been associated with multiple choroidal hypopigmented lesions and uveitis, although the majority of cases present with typical herpes zoster ophthalmicus skin rashes [7, 8]. Shields et al. [9] reported on 4 patients without active oncologic diseases presenting with choroidal vitiligo masquerading as choroidal nevi. However, when comparing to our patient presenting with multifocal bilateral choroidal depigmentation that appeared to progress on therapy and stabilize with cessation, correlation with Ipi/Nivo treatment appears more likely. The majority of previously reported cases of choroidal vitiligo have been asymptomatic, with normal visual acuity and retinal anatomy. It is therefore notable

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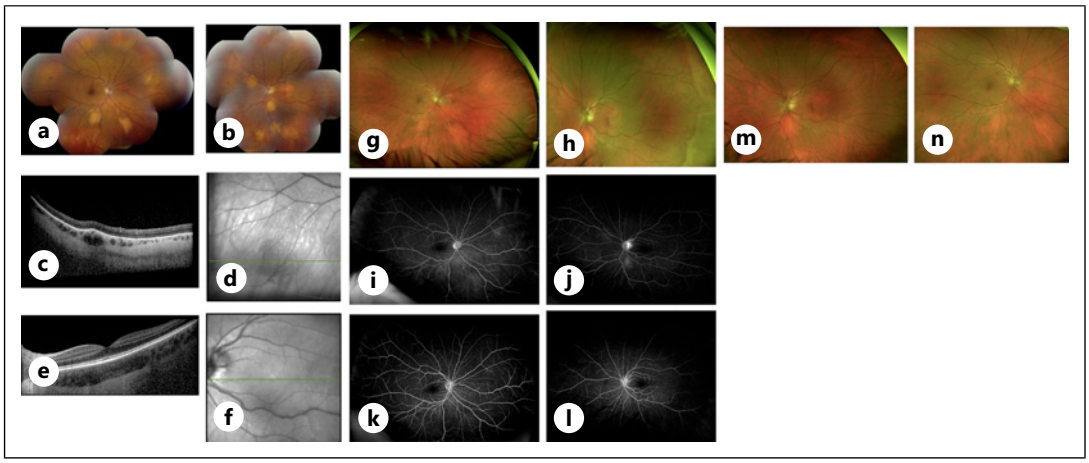

Fig. 2. Imaging at presentation, 7 months' follow-up, and 20 months' follow-up. **a**, **b** Fundus photos of OD and OS at presentation with BCVA of 20/20 and 20/25, respectively. Note the multiple hypopigmented lesions 1–3 DD in size OU with increased view of underlying choroidal vessels. **c** OD OCT at presentation that shows choroidal hyperreflectivity without retinal elevation. **d** Infrared image at presentation with green line indicating location of OD OCT. **e** OS OCT of macula at presentation. **f** Infrared image at presentation with green line indicating location of OS OCT. **g**, **h** Choroidal lesions at 7 months with increased blanching approximately 1–3 DD in size OU even 6 months after cessation of Ipi/Nivo. **i**–**l** Angiography at 7 months showing early window defects through choroidal lesions with normal perfusion and no evidence of vasculitis (**l**, **k** are OD and **j**, **l** are OS). **m**, **n** Stable choroidal lesions OU at 20 months without any changes in vision.

that our patient presented with symptoms of floaters without any attributable cause apart from her choroidal changes and poliosis without cutaneous vitiligo. These imply a potentially similar but distinct mechanism of choroidal change. Other ocular manifestations that have been reportedly induced by checkpoint inhibitors and may present as choroidal lesions include sarcoid choroidal granulomas and chorioretinal scarring [10, 11]. In contrast to the case presented here, one prior report on checkpoint inhibitor-related ocular depigmentation described leptochoroid with sparing of the RPE, significant progression of depigmentation over the observation period, late-onset poliosis and vitiligo, and lack of visual symptoms [12]. With the increasing use of immune checkpoint inhibitors in patients with various cancers, physicians should be aware of potential ocular manifestations such as the case presented. Little is still known about the long-term impact of these ocular manifestations, so we need to be more vigilant in identifying and reporting these findings. Additionally, this case exposes an underlying need for us to better understand the basic science behind checkpoint inhibitor-induced ocular toxicity, as this type of research will shed light on potential strategies to prevent or treat these side effects. As these side effects are more widely recognized and studied, we can better understand their long-term prognosis and effect on patients' vision.

Conclusion

In summary, we present a case of vitiligo-like loss of pigmentation in the RPE and choroid of a patient with multi-metastatic cutaneous melanoma receiving ipilimumab and nivolumab combination therapy. Our patient exhibited progression of depigmented lesions while on this therapy, and stabilization of lesions and vision upon cessation of therapy, even at extended

follow-up visits. Patients with cutaneous melanoma treated with novel checkpoint inhibitor immunotherapies may develop symptomatic, vitiligo-like depigmentation of choroid and RPE, which can persist even after cessation of therapy.

Statement of Ethics

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

Conflict of Interest Statement

Shildkrot: advisory board: Castle Biosciences and employee: Genentech/Roche. The following authors have no financial disclosures: C.C., A.C., and M.H.

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Author Contributions

All authors attest that they meet the current ICMJE criteria for authorship. C.C. wrote manuscript with input from A.C., M.H., and Y.S. C.C. formatted images.

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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