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Multiple evanescent white dot syndrome-like reaction associated with ipilimumab and nivolumab immune checkpoint inhibitor therapy for metastasis of choroidal melanoma

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ABSTRACT

Purpose: To present a rare case of multiple evanescent white dot syndrome (MEWDS)-like presentation associated with immune checkpoint inhibitor therapy for metastatic choroidal melanoma.

Observations: A 67-year-old non-myopic Caucasian female presented with bilateral worsening vision, flashes, and floaters after receiving two doses of ipilimumab and nivolumab for metastatic class 2 peripheral choroidal melanoma. Fundus imaging of the right eye revealed hypopigmented, extra-foveal scattered chorioretinal lesions with foveal granularity. Fluorescein angiogram and autofluorescence of the right eye demonstrated corresponding hyperfluorescent and hyperautofluorescent lesions in a wreath-like configuration. Optical coherence tomography of the right eye revealed subretinal fluid. Due to concurrent systemic side effects, checkpoint inhibitor therapy was paused and the patient was started on oral prednisone. At her one month follow up visit, her vision in her right eye returned to baseline and subretinal fluid resolved.

Conclusions: This is the first reported case of a MEWDS-like chorioretinopathy after two cycles of ipilimumab/nivolumab therapy for metastatic choroidal melanoma. As immune checkpoint inhibitor therapy is still an evolving field, more research is needed to characterize ocular side effect profiles of these agents.

1. Introduction

Immune checkpoint inhibitors have gained popularity as an effective treatment for metastatic melanoma. These immunotherapy drugs target the programmed death protein (PD-1), programmed cell death ligand 1 (PDL-1), and the cytotoxic T lymphocyte associated antigen 4 (CTLA-4) to upregulate the immune response against malignant cells. Ophthalmic side effects include dry eye in up to 24% of patients. Serious adverse reactions are uncommon, with uveitis documented in 1% of patients including cases of panuveitis, VKH-like reaction, or inflammatory chorioretinopathy.[1,2] Large systematic reviews have occasionally reported neuro-ophthalmologic side effects including myasthenia, inflammatory orbitopathy, optic neuropathy, or cranial nerve palsy.[3,4] Retinal side effects are extremely rare and only a few cases of serous retinal detachment, exudative retinal detachment, atypical choroidal lesions, and immune retinopathy associated with immune checkpoint inhibitors have been described.[1,2,5]

The majority of literature regarding the use of these drugs in melanoma has been reported on patients with cutaneous melanoma rather than the much more rare uveal melanoma.[1] It remains unclear whether the frequency of ocular side effects changes if these agents are used in this population. We present a patient with a chorioretinopathy pattern resembling multiple evanescent white dot syndrome (MEWDS) after starting ipilimumab (anti-CTLA4) and nivolumab (anti-PD1) for metastatic choroidal melanoma.

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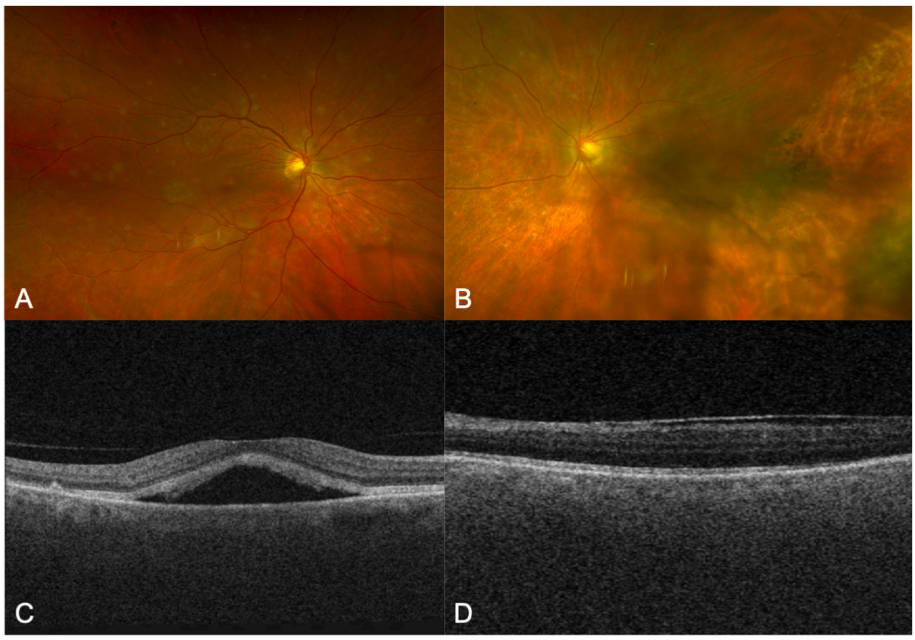

Fig. 1. Fundus photography of central macula of right eye (A) showing chorioretinal inflammatory lesions. Fundus photography of central macula of the left eye showing a scar from prior radioactive plaque placement. Triton OCT of right eye (C) showing outer retinal disturbance in area of lesions and subretinal fluid. Triton OCT of left eye (D) does not demonstrate subretinal fluid.

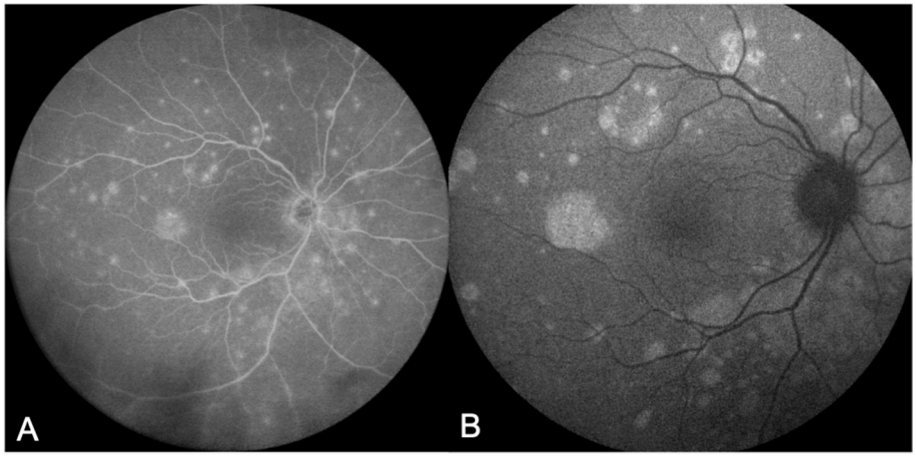

Fig. 2. Late-stage fluorescein angiography of the right eye showing early hyperfluorescence of chorioretinal lesions in a wreath-like pattern. Ring-like staining is noted superotemporally to the optic disc (A). Autofluorescence image of the right eye showing hyperautofluorescence of chorioretinal lesions in a wreath-like pattern (B).

1.1. Case

A 67-year-old non-myopic Caucasian woman presented with bilateral worsening vision, flashes, and floaters after receiving two doses of immune checkpoint inhibitor therapy. Two years earlier, she underwent I-125 plaque brachytherapy for a medium-size Class 2 peripheral choroidal melanoma in the left eye with tumor height of 8.66mm. Two months prior to presentation, she began treatment with ipilimumab (3mg/kg) and nivolumab (1mg/kg) for a biopsy-confirmed hepatic metastasis. She denied having a flu-like illness recently.

On presentation, her best corrected visual acuity in her right eye decreased to 20/60 from a baseline of 20/20. Best corrected visual acuity in the left eye, limited by macular atrophy, decreased to 20/200 from a baseline of 20/70. Anterior segment examination revealed 1–2 cells per high power field in the right eye and normal findings in the left eye. Examination of the vitreous was unremarkable. Fundus examination in the right eye revealed faint hypopigmented scattered chorioretinal lesions with foveal granularity (Fig. 1A). Fundus examination in the left eye revealed the regressed choroidal melanoma and scarring from brachytherapy (Fig. 1B). Fluorescein angiogram (FA) of the right eye demonstrated punctate leakage resulting in early hyperfluorescence from chorioretinal lesions in a wreath-like pattern (Fig. 2A). FA of the left eye demonstrated staining of the scarred chorioretinal area from brachytherapy. Fundus autofluorescence of the right eye demonstrated hyperautofluorescence of chorioretinal lesions in a wreath-like pattern (Fig. 2B). Optical Coherence Tomography (OCT) revealed a small pocket of subfoveal fluid in the right eye and a baseline epiretinal membrane in the left eye (Fig. 1C and D). Visual field testing and Indocyanine Green Angiography (ICG) were not obtained.

Given the presence of concurrent systemic adverse side effects secondary to checkpoint inhibitor therapy, the treating oncologist paused ipilimumab and nivolumab and started oral prednisone. The patient was

instructed to take 60mg daily but instead took 20mg daily. The patient was also started on prednisolone acetate four times daily in the right eye for anterior segment inflammation. At one month follow-up, best corrected visual acuity improved to 20/25 in her right eye. Exam of the right eye showed decreased subretinal fluid and decreased areas of hypopigmentation seen on fundus photography. Her exam and vision in the left eye were unchanged. Ipilimumab and nivolumab were not restarted due to persistent extraocular side effects.

2. Discussion

We present a novel case of MEWDS-like chorioretinopathy after two cycles of treatment with immune checkpoint inhibitors. MEWDS represents a self-resolving inflammatory chorioretinopathy that commonly presents unilaterally in a young healthy myopic female after a flu-like illness with worsening vision and enlargement of the blind spot. While this patient's demographic and subretinal fluid on OCT differs from typical MEWDS, her pattern of foveal granularity and multiple extrafoveal areas of hypopigmentation with corresponding early hyperfluorescence on FA and hyper-autofluorescence in a wreath-like pattern in the right eye resembles classic findings of the disease.[6]

To our knowledge, the only previously reported case of inflammatory chorioretinopathy associated with immune check-point inhibition was a patient with birdshot-like chorioretinopathy after pembrolizumab therapy which resolved after intravitreal steroid injection.[2]

Of note, this patient's reaction may also be explained by a VKH-like reaction or panuveitis, given the presence of subfoveal fluid. Both reactions are more common complications compared to inflammatory chorioretinopathy following immune checkpoint inhibitors with a recent review of the literature identifying 126 cases of uveitis following immune checkpoint inhibitor. Fifteen of these 126 cases, presented with VKH-like reactions following initiation of either ipilimumab, and nivolimumab, their combination, or pembrolizumab.[7] In the absence of ICG angiography and further uveitis workup, we cannot exclude the presence of these reactions with or without inflammatory chorioretinopathy. However, unlike previous cases of VKH-like serous detachments, this patient had only a minimal subfoveal fluid pocket. In addition, the lack of bilateral presentation, neurological and integumentary symptoms, and extensive multifocal areas of pinpoint leakage on FA differ from what is commonly seen in VKH.[8] In summary, both clinical and imaging findings are in line with a MEWDS-like reaction rather than a VKH-like reaction.

We hypothesize that the hyperactive immune response induced by the immune checkpoint inhibitors triggered the patient's development of an inflammatory chorioretinopathy in the right eye. This is consistent with the presumed inflammatory or auto-immune etiology behind MEWDS and may explain the atypical demographics of this patient. This is further supported by the patient's rapid improvement one month after treatment cessation and oral prednisone.

The etiology of this patient's worsening vision in the left eye remains unclear given a lack of imaging evidence for an inflammatory chorioretinopathy. Furthermore, lack of improvement in visual acuity with treatment cessation and oral prednisone may suggest a non-inflammatory cause such as complications of prior choroidal melanoma treatment.

Many previous reports of ocular side effects with immune checkpoint inhibitors occurred in patients being treated for cutaneous melanomas or other non-ocular malignancies. Because of the relative paucity of retinal side effects of these agents in addition to the fact that there are approximately only 2000 cases of choroidal melanoma diagnosed in the United States each year, retinal side effects of immune checkpoint inhibitors in metastatic choroidal melanoma is very rare.[9] More research is needed to determine whether there is increased risk for retinal side effects in patients with choroidal melanomas.

Despite this patient's atypical demographic and presence of subretinal fluid, the imaging evidence and clinical course in this case is suggestive of a MEWDS-like chorioretinopathy. Physicians should be wary of MEWDS-like inflammatory reactions in patients being treated with immune checkpoint inhibitor therapy.

3. Patient consent

The patient consented to publication of the case in writing/orally.

This study was exempt under the UVA Institutional Review Board Guidelines.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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