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Pigmentary retinopathy associated with immune therapy for advanced cutaneous melanoma

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ABSTRACT

Purpose: To describe a case of bilateral retinal pigmentary changes in the setting of immune checkpoint inhibitor therapy (ICIT).

Observations: A 69-year-old man with a history of advanced cutaneous melanoma was started on combination ICIT with nivolumab and ipilimumab and stereotactic body radiation therapy. Soon after, he developed photopsias and nyctalopia with findings of discrete retinal pigmentary changes bilaterally. Initial visual acuities were 20/20 and 20/30 in the right and left eye, respectively. Multi-modal imaging revealed sub-retinal deposits with progressive changes in pigmentation and autofluorescence, associated with decreased peripheral fields on formal perimetry. A full-field electroretinogram revealed attenuated and delayed a- and b-waves. Positive serum retinal autoantibodies were identified. The patient developed left-sided optic nerve edema and center-involving cystoid macular edema which improved after treatment with sub-tenon's triamcinolone.

Conclusions: The use of ICIT has greatly expanded in oncologic practice with subsequent increases in immune related adverse events that pose significant systemic and ophthalmologic morbidities. We propose that the new retinal pigmentary changes seen in this case are the sequelae of an autoimmune inflammatory response against pigmented cells. This adds to the rare side effects that may occur after ICIT.

1. Introduction

Immune checkpoint inhibitor therapy (ICIT) has emerged as the standard of care in the management of several primary and metastatic malignancies.[1] The combination of nivolumab and ipilimumab, in particular, is one of the first-line treatments for advanced cutaneous melanoma.[2] These agents directly bind to selective T-cell membrane receptors preventing tumor induced T-cell deactivation.

Ipilimumab is a monoclonal antibody directed towards the cytotoxic T-lymphocyte antigen-4 (CTLA-4) receptor, which inhibits binding of B7 ligands on T-cell membranes, which in turn binds to CD28, subsequently inducing T-cell activity. Similarly, nivolumab is a monoclonal antibody directed towards the programmed death-1 (PD-1) receptor which prevents receptor binding by tumor cells expressing programmed death-1 ligand (PD-1) that would otherwise induce immune cell deactivation.[1,3] Together, they are effective in blocking inhibitory pathways and promoting host immune responses. Combination therapy has been shown to significantly increase survival rates over monotherapy with either agent alone.[2]

Both nivolumab and ipilimumab are known to cause immune-related adverse events (irAEs), particularly when used in combination. Nearly 60% of patients receiving combination therapy and 20–30% of patients receiving PD-1 monotherapy will require immunosuppression.[2] In contrast, the incidence of ophthalmologic irAEs is relatively low, affecting only 1% of patients, although this is likely under-reported due to the lack of baseline ophthalmologic evaluation and testing.[3] With combination ICIT established as the preferred initial treatment for advanced cutaneous melanoma irrespective of *BRAF* status, the body of literature regarding ocular irAEs is steadily expanding.[4] The ophthalmologic irAEs span a remarkably wide gamut, ranging from mild ocular surface dysfunction such as superficial punctate keratitis and conjunctivitis to severe posterior involvement with significant vision loss in the form of cystoid macular edema (CME), serous retinal detachments, birdshot chorioretinopathy, optic neuritis, and Vogt-Koyanagi-Harada (VKH) like syndromes among others.[5–13]

Given the relatively low incidence of ophthalmologic irAEs, new clinical presentations of sequelae from ICIT could help establish a diagnosis and expedite treatment to decrease morbidity. Herein, we

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present a case of autoimmune retinopathy (AIR) after initiation of ICIT in a patient with advanced cutaneous melanoma, with a presentation of bilateral retinal pigmentary changes to expand the clinical phenotypes of irAEs.

2. Case report

A 69-year-old male with a history of cutaneous melanoma initially diagnosed in 2007 on his right shoulder was found to have biopsy proven recurrence in 2021 with metastatic lesions to the liver, brain, spleen, bone, and left orbit (lateral rectus). The patient was initiated on nivolumab and ipilimumab combination therapy in November 2021. Following two cycles of induction, he underwent five fractions of stereotactic body radiotherapy to a total dose of 30 Gy to the L1-L3 spine and left orbit which was completed in January 2022. He received an additional two cycles of nivolumab and ipilimumab before transitioning to nivolumab maintenance therapy in March 2022. His medical course was complicated by immune checkpoint inhibitor induced type 1 diabetes mellitus, thyroiditis and vitiligo.

The patient was referred to the retina service by medical oncology for complaints of photopsias and nyctalopia that began in December 2021, approximately one month after initiating ICIT. His previous ocular history was significant for cataract surgery performed in both eyes in October 2021 with no reports of abnormal posterior findings on review of his pre-operative clinic visit documentation. At his initial retina evaluation in March 2022, he was found to have 20/20 and 20/30 vision in the right (OD) and left (OS) eyes, respectively. His intra-ocular pressures were normal bilaterally and slit lamp examination was unremarkable except for posterior chamber intraocular lenses with posterior capsular opacifications bilaterally. His dilated fundus examination showed a pale fundus with discrete pigmentary changes involving the macula and periphery bilaterally (Fig. 1A and B). The lesions closer to the posterior pole appeared as lightly pigmented clumps, which increased in pigmentation towards the periphery. There was a reversed pattern demonstrated on fundus auto-fluorescent (FAF) images (Fig. 1C and D). The lightly pigmented clumps on ultra-widefield (UWF) imaging around the arcades and peripapillary region appeared hyper-autofluorescent on FAF (Fig. 1E and F arrows). These clumps increased in pigmentation on UWF images as they progressed through the mid-periphery towards the far periphery and appeared hypo-autofluorescent on FAF (Fig. 1E and F arrowheads).

FAF imaging did not show areas of generalized reduced hypo-autofluorescence suggestive of retinal pigment epithelium (RPE) atrophy. Macular spectral domain optical coherence tomography (SD-OCT) found trace extra-foveal CME in the right eye (Fig. 2A). Sub-retinal hyper-reflective deposits which corresponded with focal lesions with increased reflectance on infra-red imaging were found along the arcades bilaterally (Fig. 2C and D).

At his six-month follow up in September 2022, OD vision remained stable at 20/20 whereas OS vision had decreased to 20/200. Fundus examination OD showed stable trace macular edema on OCT imaging. However, OS examination demonstrated significant macular and optic nerve edema with hemorrhage and associated foveal-involving CME (Fig. 3B and E). Formal perimetry demonstrated constricted peripheral fields in both eyes with an enlarged blind spot in the left eye (Fig. 3C and D). His optic nerve edema was not thought to be due to a primary optic nerve etiology given the absence of a relative afferent pupillary defect in either eye, following neuro-ophthalmology review. His color testing by Ishihara color plates, however, was found to be 7/8 OD and 1/8 OS (control plate only). Repeat MRI imaging performed in October 2022 showed stable findings with no enlargement of the orbital mass or evidence of optic nerve compression. Follow up fluorescein angiogram demonstrated normal choroidal and arterio-venous phases, transmission defects with left optic disc leakage, and similar hyper-fluorescent patterns as seen on FAF (Fig. 4). A full-field electroretinogram (ERG) indicated attenuated and delayed a- and b-wave responses in both photopic and scotopic testing.

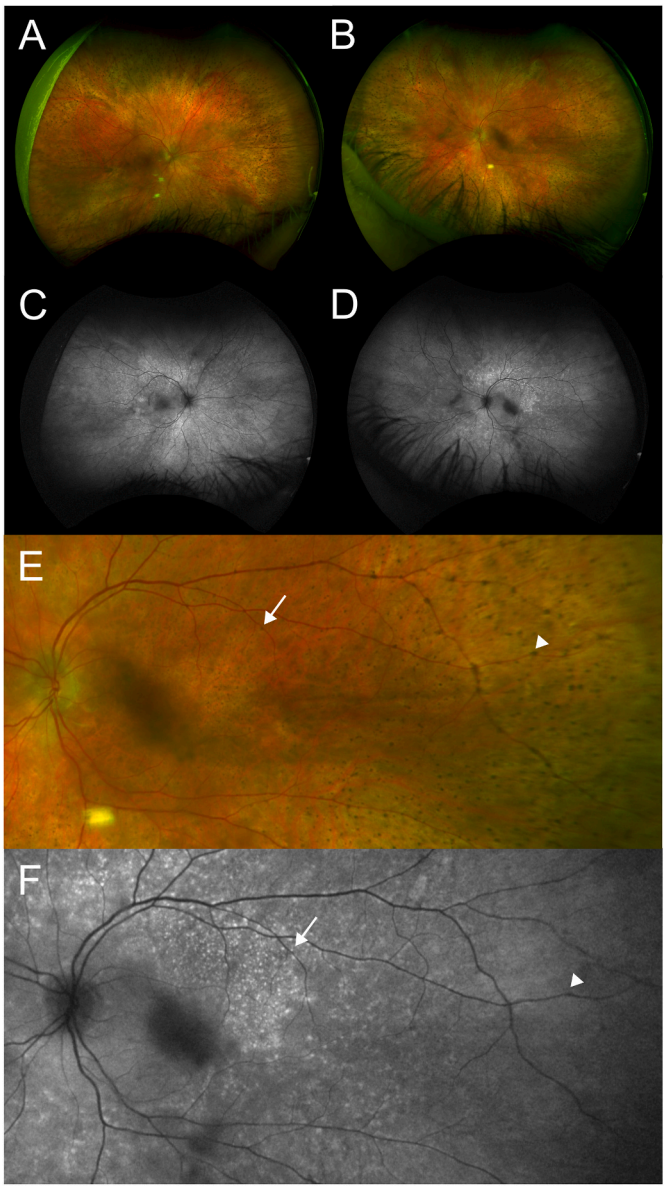

Fig. 1. Fundus Imaging
Ultra-widefield (UWF) pseudo-color images demonstrate pigmentary deposits in the right (A) and left (B) eyes. Corresponding fundus auto-fluorescence (FAF) images show hyper-autofluorescent deposits in the right (C) and left (D) eyes in proximity to the temporal arcades. A magnified UWF pseudo-color image of the left eye (E) shows lightly pigmented clumping (arrow) and darkly pigmented clumping (arrowhead). A magnified FAF image of left eye (F) with hyper-autofluorescent deposits (arrow) and hypo-autofluorescent deposits (arrowhead). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Due to his deteriorating vision, the patient's oncologic team was consulted for a trial of treatment discontinuation. His consistent clinical and radiographic responses indicated a good oncologic prognosis, and the patient's maintenance nivolumab was held. Immunotherapy was resumed approximately six weeks later due to a lack of significant subjective or objective ophthalmologic change.

In view of the unclear etiology and photopsias, an AIR panel was ordered in November 2022 and found positive for retinal autoantibodies towards carbonic anhydrase II, recoverin, TULP1, and TRPM1. Immunohistochemical staining was positive for both photoreceptor and bipolar cells. Treatment with multiple injections of sub-tenons

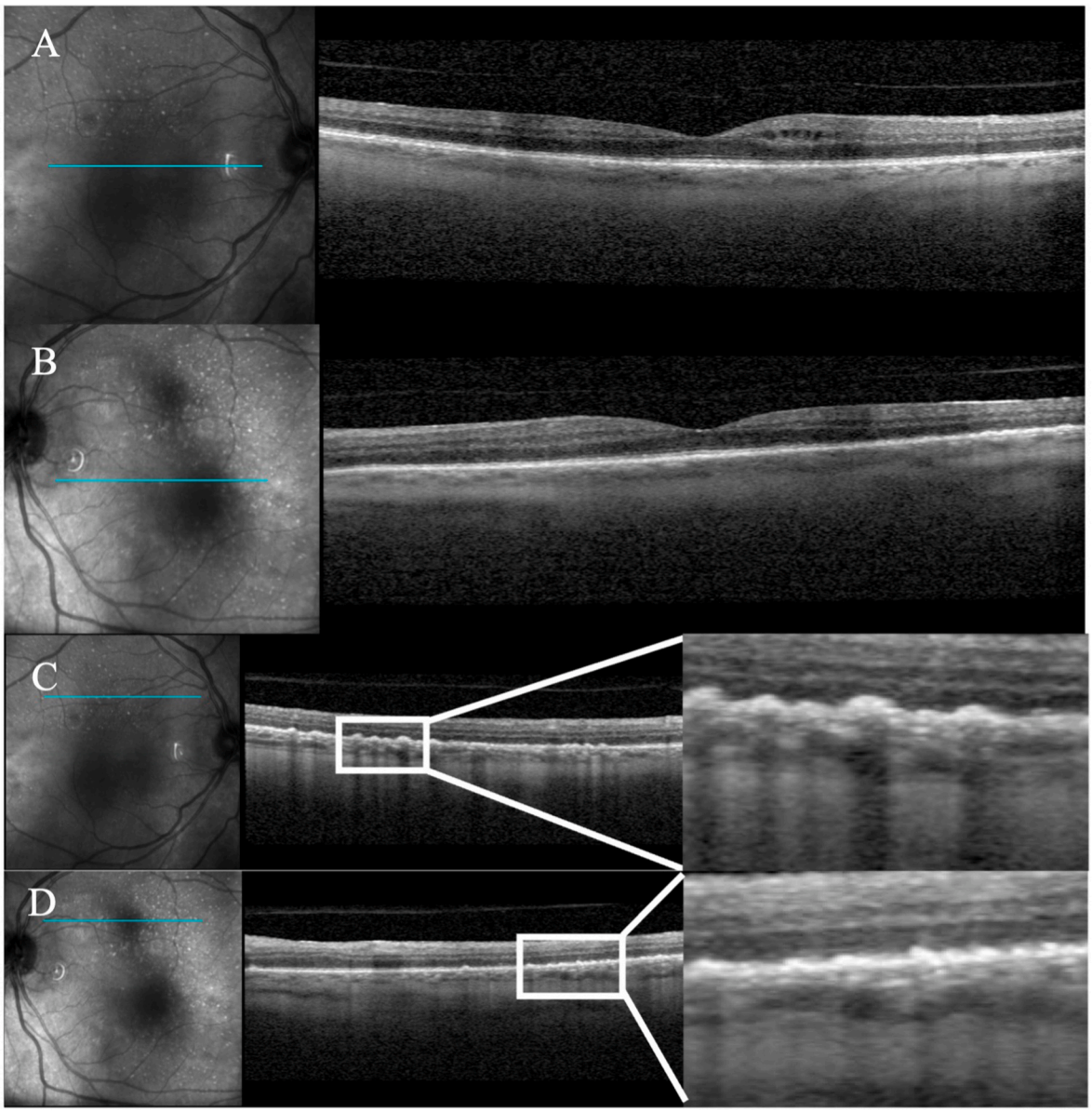

Fig. 2. Optical Coherence Tomography Imaging
Foveal-centered spectral-domain optical coherence tomography (SD-OCT) image of right eye (A) with extra-foveal cystoid macular edema (CME) and a normal SD-OCT image of left eye (B). Superior macular SD-OCT image of right eye with magnified section of outer retinal layers (C) showing sub-retinal hyperreflective deposits with central shadowing. Superior SD-OCT image of left eye with magnified section of outer retinal layers (D) showing sub-retinal hyperreflective deposits with central shadowing.

triamcinolone in the left eye led to subsequent improvement of edema and vision to 20/63, suggesting an immune related etiology to the edema (Fig. 3F and G).

3. Discussion

The present case report of bilateral discrete pigmentary retinal changes highlights an unusual presentation of irAEs from checkpoint inhibitors in the setting of AIR. Overall, a low incidence of ophthalmologic irAEs, combined with the lack of baseline ophthalmologic evaluation, make a definitive causal relationship between activation or recurrence of AIR and ICIT difficult to establish. Patients do not routinely undergo serological testing for retinal autoantibodies and/or evaluation by ophthalmology prior to starting ICIT. The lack of routine evaluation has led to suggested screening practices for a broad range of pharmacotherapeutics including nivolumab and ipilimumab. Recommendations include dilated fundus exams, color fundus photography, and OCT imaging every 3–6 months, with an aim to promote a collaborative inter-disciplinary approach to reduce morbidity.[14] The predominant use of ICITs such as nivolumab and ipilimumab for advanced cutaneous melanoma may increase the prevalence of significant visual morbidity. The wide range of clinical presentations combined with potentially controversial management choices in the setting of potentially life-prolonging therapies, makes expedited diagnosis and treatment prudent, particularly for inter-disciplinary discussions.

Our patient reported bilateral photopsias and nyctalopia approximately one month after initiation of nivolumab and ipilimumab consistent with the presentation of symptoms and timeline of onset for AIR, per prior reports.[15] Recent literature has elucidated a possible relationship between nivolumab and ipilimumab with AIR, first reported by Kim et al. and expanded upon in a case series and systematic review.[3,15] Heng et al. reviewed 14 previously published cases of AIR

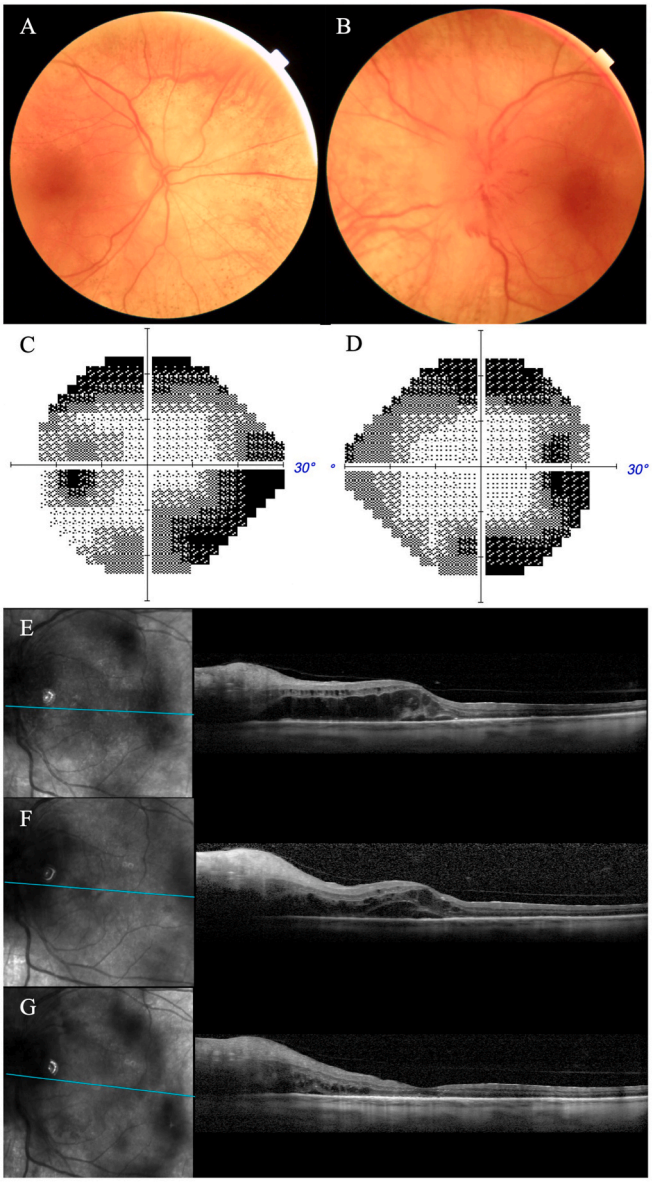

Fig. 3. Optic Nerve Imaging and Evaluation
Optic nerve of normal right (A) with edema and hemorrhage of the left (B) eye. Humphrey visual field 24–2 of the left (C) and right (D) eyes with peripheral field defects. Foveal centered SD-OCT image of left eye prior to (E), one month after (F), and two months after (G) treatment with sub-tenons triamcinolone.

associated with advanced cutaneous melanoma in which they described a spectrum of retinal findings from melanoma associated retinopathy based on characteristic ERG findings of an electronegative b-wave with anti-retinal antibodies to acute exudative polymorphic paraneoplastic vitelliform maculopathy.[15] Throughout the course of his evaluation, the patient developed other previously documented irAEs including CME, optic nerve edema, and anterior uveitis of both eyes, albeit in the setting of discrete bilateral pigmentary changes in the macula and periphery.

Testing in our patient also identified retinal autoantibodies to carbonic anhydrase II, recoverin, TRPM1, and TULP1 as well as immunohistochemical staining of both photoreceptor and bipolar cells. However, AIR and its paraneoplastic counterparts, which include cancer associated retinopathy (CAR) and melanoma associated retinopathy (MAR), and non-paraneoplastic classifications have been documented since the 1980s, and do not typically present with discrete pigmentary changes, as seen with this patient.[15,16] Many tumors, including melanoma, are associated with multiple retinal antibodies.[17,18] Specifically, TRPM1, enolase, and aldolase have been closely associated with melanoma.[19–21] Funduscopic changes of AIR are characteristically unremarkable at presentation but have been documented to change over time and include vascular attenuation, diffuse chorioretinal atrophy, and retinal pigment epithelium mottling.[22] Full-field ERG of our patient demonstrated attenuated a- and b-waves more consistent with CAR and cases of non-paraneoplastic AIR rather than MAR which classically exhibit electronegative b-waves.[17,18,22]

The previous reports of AIR did not note any pigmentary retinopathies. Notably, our patient's fundus examination, prior to his cataract surgery in 2021, before initiating ICIT, was normal. While still not fully understood, the postulated mechanisms behind systemic irAEs may provide insight into the pigmentary clumps seen in our patient, as well as the other ophthalmologic irAEs, most notably the VKH-like syndromes. Systemic irAEs from nivolumab and ipilimumab most commonly present as gastrointestinal toxicity, endocrinopathies, and dermatologic manifestations, corresponding with our patient's development of type 1 diabetes mellitus, thyroiditis and vitiligo. The mechanisms are thought to be due to increased T-cell activity towards both host and cancer antigens, increased levels of pre-existing autoantibodies, and subsequent downstream cytokine- and complement-mediated inflammation.[23] Thus, it is logical to suggest that when nivolumab and ipilimumab blocks the natural competitive inhibitor of T-cell stimulation, it can also stimulate T-cell targeting towards both host and cancerous melanocytic antigens in the body. Witmer had previously posited this theory to explain the similar findings between VKH disease and ICIT induced VKH-like syndromes.[5] The concept that melanoma antigens are the same as those targeted in melanocyte-related autoimmune disease, including VKH and sympathetic ophthalmia, led to the discovery of melanoma antigen recognized by T cells 1 (MART-1), as well as tyrosinase related protein (TRP) 1 and TRP 2, in addition to other proposed antigens including those against photoreceptors, Müller cells, lens epithelium derived growth factor, and uveal autoantigen, all thought to play a role in the mechanism of VKH. Unsurprisingly, T-cells targeting self-antigens, such as tyrosinase expression by melanocytes in various organs, can result in multisystem acute autoimmune disease as previously described.[24]

It is notable that the pigmentary findings in our patient are different from classical VKH or VKH-like syndromes, regardless of whether they were associated with melanoma, either with or without ICIT use.[5,16,25–30] This raises the possibility an alternative mechanism. The patient's radiation therapy may have caused a breakdown of the blood-retinal barrier, with a cellular inflammatory response occurring in the outer retina. Although there are no studies evaluating the integrity of the blood-retina barrier with respect to radiation doses, it is known that breakdown of the blood-brain barrier occurs as low as 10 Gy.[31] As such, a damaged blood-retina barrier with outer retinal inflammation impacting the photoreceptors could activate microglial phagocytosis of rod outer segments with resultant sub-retinal accumulation and also result in RPE migration.[32] This would explain the otherwise intact RPE seen on OCT and relatively normal FAF suggesting that RPE is not completely lost, as can be seen in some RPE disease, such as geographic atrophy in age-related macular degeneration. Other possible etiologies for the pigmentation include melanoma metastases, however, these would more likely be choroidal and unlike the sub-retinal deposits seen in our patient.

4. Conclusion

The present case is an unusual presentation of bilateral pigmentary retinopathy and AIR in the spectrum of ophthalmologic irAEs, concurrent with starting ICIT in advanced cutaneous melanoma. We propose an etiology based upon an inflammatory immune response. Further research into systemic and ophthalmologic irAEs should be pursued given the significant morbidity of ICIT as well as the potential to inform subsequent management decisions.

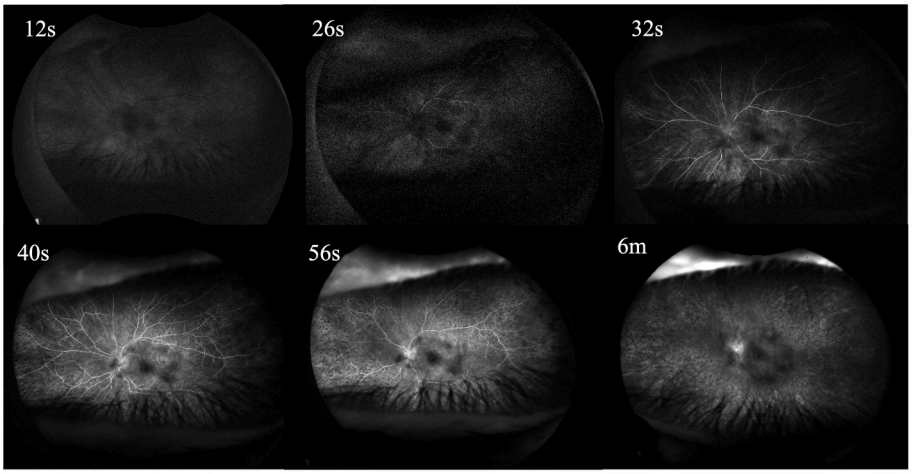

Fig. 4. Fluorescein Angiography
Fluorescein angiogram images of the left eye taken at: 12 seconds, 26 seconds, 32 seconds, 40 seconds, 56 seconds and 6 minutes.

Patient consent

The study was approved by the Institutional Review Board of the University of California, San Diego (UCSD) for a waiver of consent, due to the retrospective nature of the study data. Patient data was masked, and consenting was practiced in accordance with institutional policies set within the department. This report and all methodologies used adhered to the tenets of the Declaration of Helsinki. The case report does not contain any identifying information.

Disclosures

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The other authors declare no conflict of interest, no funding, or grant support. All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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