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Video

Anti-TRPM1 autoantibody-positive unilateral melanoma associated retinopathy (MAR) triggered by immunotherapy recapitulates functional and structural details of *TRPM1*-associated congenital stationary night blindness

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ABSTRACT

Purpose: To describe the retinal phenotype of an unusual case of anti-TRPM1 autoantibody-positive unilateral melanoma-associated retinopathy (MAR) triggered by nivolumab therapy and compare with the phenotype of *TRPM1*-associated Congenital Stationary Night Blindness (*TRPM1*-CSNB).

Observations: Unilateral MAR was diagnosed 3 months after starting nivolumab therapy for consolidation of a successfully treated melanoma. Retinal autoantibodies against TRPM1 were identified. ffERG, microperimetry and static chromatic perimetry confirmed unilateral ON-Bipolar Cell (ON-BPC) dysfunction and central rod sensitivity losses in the left eye; the contralateral eye was normal. There was borderline ganglion cell (GCL) and inner nuclear layer (INL) thinning, but a significantly thinner inner plexiform layer (IPL) in the affected compared to the unaffected eye. Longitudinal reflectivity profiles (LRPs) demonstrated an abnormal inner plexiform layer (IPL) lamination in the involved eye. Nearly identical changes were documented in two cases of *TRMP1*-cCSNB and in a case of anti-TRPM1 autoantibody-negative MAR. The functional changes partially recovered with discontinuation of the medication without added immunosuppression.

Conclusions and Importance: Comparisons between the affected and unaffected eye in this unilateral MAR case revealed inner retinal abnormalities and abnormal lamination of the IPL associated with the classical retina-wide ON-BPC dysfunction, and localized central rod-mediated sensitivity losses. A nearly identical structural phenotype in two cases of cCSNB and a case of anti-TRPM1 autoantibody-negative MAR supports a specific structural-functional phenotype for these conditions with ON-BPC dysfunction.

1. Introduction

Melanoma associated retinopathy (MAR) is an infrequent paraneoplastic condition characterized by an acute or subacute onset of nyctalopia, photopsias and/or visual field defects, and a distinctive pattern by electroretinography, traditionally associated with cutaneous, ocular, systemic melanoma, or melanomas of unknown origin.[1–9] The fundus exam and optical coherence tomography (OCT) imaging are usually unremarkable, although abnormal fundus findings and inner retinal abnormalities on imaging have been reported.[10–13] The full-field electroretinogram (ERG) typically shows an electronegative waveform with abnormally reduced amplitudes of the b-wave and preserved photoreceptor a -wave amplitudes in response to bright flashes of light under scotopic conditions, reflecting ON-bipolar cell dysfunction.[3,6,14]

The trigger of autoimmunity in cancer-associated retinal ON-bipolar cell (ON-BPC) dysfunction, including in MAR, is not fully understood,

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though it may be due to molecular mimicry between tumoral and retinal antigens.[15–17] Anti-retinal autoantibodies (AAbs) against photoreceptor specific proteins, including Rhodopsin, Transducin, Recoverin, Arrestin, and against other protein antigens, such as Enolase, CAII, and Aldolase have been described.[6,18] More recently a specific AAbs against the transient receptor potential cation channel, subfamily M, member 1 (anti-TRPM1) has been identified in a subset of MAR cases.[10,19–24] TRPM1, or melastatin, is a 180-kDa transmembrane protein that localizes to the dendritic tips, cell bodies and axons of bipolar cells, involved in synaptic transmission between photoreceptors and ON-BPCs.[24–27] The protein is a nonselective cation channel negatively regulated by the ON-BPC metabotropic glutamate receptor 6 (GRM6) and a G protein complex (Go) signaling cascade.[25,28] Of relevance to this work, recessively inherited mutations in *TRPM1* lead to a similar ON-BPC dysfunction phenotype clinically known as complete stationary night blindness (cCSNB).[29]

MAR may precede or follow for nearly two decades the primary diagnosis of melanoma, is usually a bilateral condition, and has been rarely associated to immunotherapy.[30,31] Herein, we present a case of unilateral anti-TRPM1-MAR triggered by immunotherapy used for consolidation of remission of a successfully treated metastatic cutaneous melanoma. To gain a better understanding of the pathophysiology and management of autoimmune retinopathies (AIRs), in particular MAR, as well as of its genetic counterpart (CSNB), we characterized in detail the structural and functional phenotype of this unusual MAR presentation and compare the findings against two patients with *TRPM1*-associated cCSNB (*TRPM1*-cCSNB).

2. Case report

A 66-year-old female with a history of cutaneous malignant melanoma presented to our practice for a retina evaluation at the request of her oncologist in early January of 2023, due to visual phenomena of swirling and shimmering lights with a haze/smoke around images. The patient had noticed a left parietal scalp lesion 17 months prior to our evaluation. A biopsy of the lesion revealed superficial spreading, ulcerated and mitogenic malignant melanoma. A wide excision and sentinel lymph node biopsy demonstrated residual melanoma (Clark level V, Breslow thickness 5.4 mm), with negative margins and negative left cervical sentinel lymph node biopsy. Pan-CT scanning was negative for any metastatic disease (stage IIc disease), so no adjuvant therapy was indicated and close monitoring for high risk of recurrence was maintained. One year following the initial diagnosis, she was found to have a 1.0 cm left neck nodule and fine needle aspiration demonstrated recurrent melanoma (stage IIIC, T4bN1b). As a result of recurrence, she was enrolled in a clinical trial. The trial protocol consisted of an

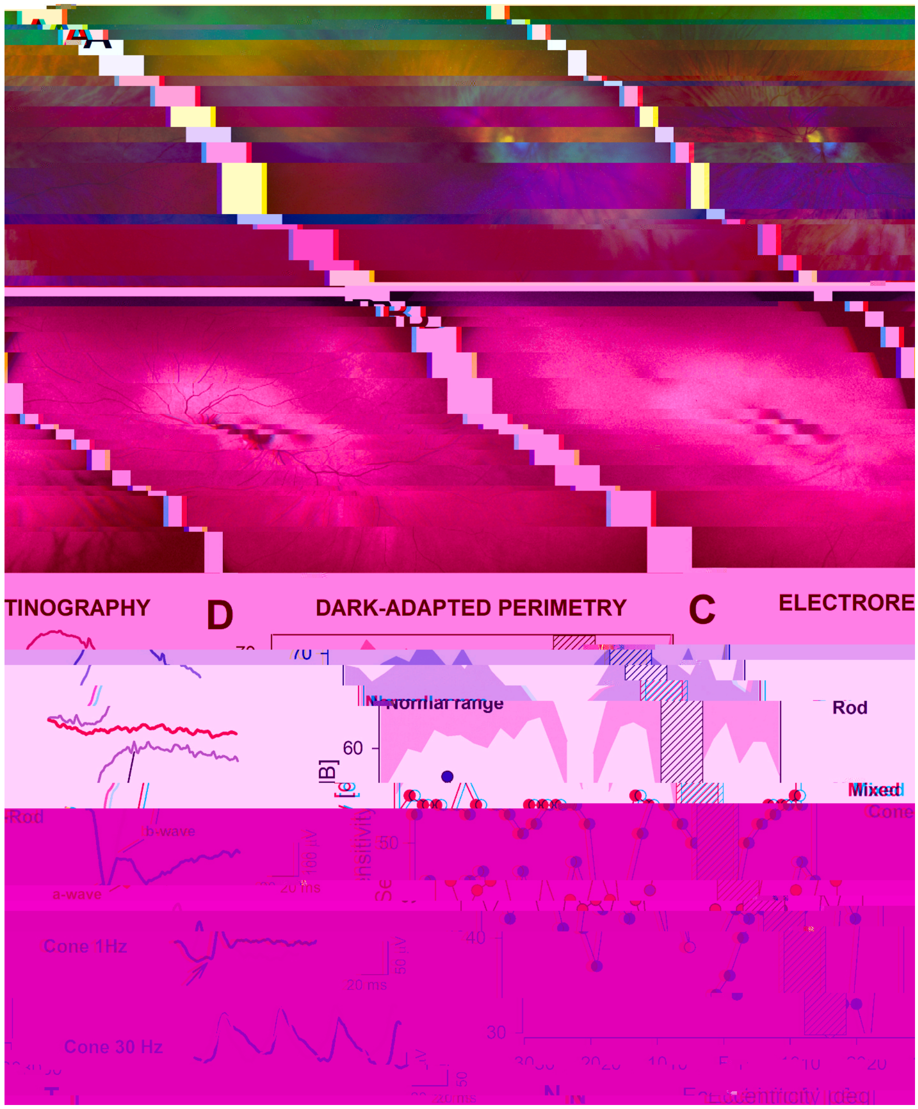

Fig. 1. A&B. Ultra wide-field (Optos, Inc., Marlborough, MA) pseudo-color fundus photography (A) and short-wavelength fundus autofluorescence (SW-FAF) (B) in the patient with TRMP1-MAR. **C.** Standard full-field ERG in the patient. Gray traces are normal responses from the right eye, red thicker traces from the left abnormal eye. The photoreceptor a-wave and the post-receptoral b-wave are labeled. Arrow in the 1Hz cone response points to a broad a-wave morphology that precedes a mildly delayed steep rise of the b-wave. Responses correspond to the following nomenclature used by the ERG program and the ISCEV standard: rod = DA 0.01, mixed cone-rod = DA 3.0, 1Hz cone = LA 3.0, 30Hz cone = LA 30Hz). . Dark-adapted two-color perimetry demonstrating reduced sensitivities in the left eye to the blue-green 500 nm (blue symbols in top trace) and red (650 nm, red symbols in bottom trace) stimuli. The spectral sensitivity differences support rod-mediation of perception in all locations and thus a rod scotoma. Hatched bar is over the location of the blind spot. N, nasal; T, temporal, visual field. Grayed band is the normal range (mean±2SD) for the blue stimulus. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

symmetric in comparison to the contralateral eye (not shown) in the anti-TRPM1-MAR patient, as well as in the *TRPM1*-cCSNB patients. Unexpectedly, there was thinning of the IPL in the pericentral retina of both the anti-TRPM1-MAR and the *TRPM1*-cCSNB patients.

To explore possible additional structural changes, longitudinal reflectivity profiles (LRPs) were extracted from a location 4° from the foveal center in the nasal retina of each eye and compared to representative normal LRPs (Fig. 2C). The normal pentalaminar structure of the histologic inner IPL corresponds to three local small LRP signal peaks interspaced by two troughs (Fig. 2C, *open circles overlapping LRP traces*).[37–41] Interestingly, the localized thinning of the GCL, IPL and INL in the affected eye of the MAR patient is associated with the loss of one of the IPL peaks, presumably the most vitread of the sublamina that corresponds to ON-BPC (Fig. 2C, *thick black* LRP trace).[41,42] The outer plexiform layer (OPL) signal appears normal. Nearly identical abnormalities were noted in the eyes of the two patients with *TRMP1*-cCSNB.

Nivolumab dosing protocol was withheld. She was seen for follow-up two weeks later at which time her subjective symptoms were mildly improved and her exam was unchanged. She presented for two more follow-up appointments: one month later and then again at three months. At both appointments, she endorsed continued improvement with significantly more manageable symptoms and less flickering photopsias in her left eye. Repeat ERG demonstrated identical photoreceptor function (a-waves) compared to baseline and marked improvement of inner-retinal responses in the left eye (Fig. 3A). Although there was still a negative configuration ERG of the mixed cone-rod response, the rod b-wave elicited with a dim flash was clearly detectable after discontinuation of the medication. The cone response regained a normal morphology. The right eye ERGs remained normal. Mesopic microperimetry (iCare Macular Integrity Assessment System, MAIA, Icare USA, Inc. Raleigh, NC), using a 10-2 protocol grid (achromatic 0.43° diameter stimulus, achromatic 1.27 cd/m^2 background), was used to document overall retinal functioning, dominated by rods in perifoveal retina, by cones at or close to fixation.[43,44] Microperimetry at

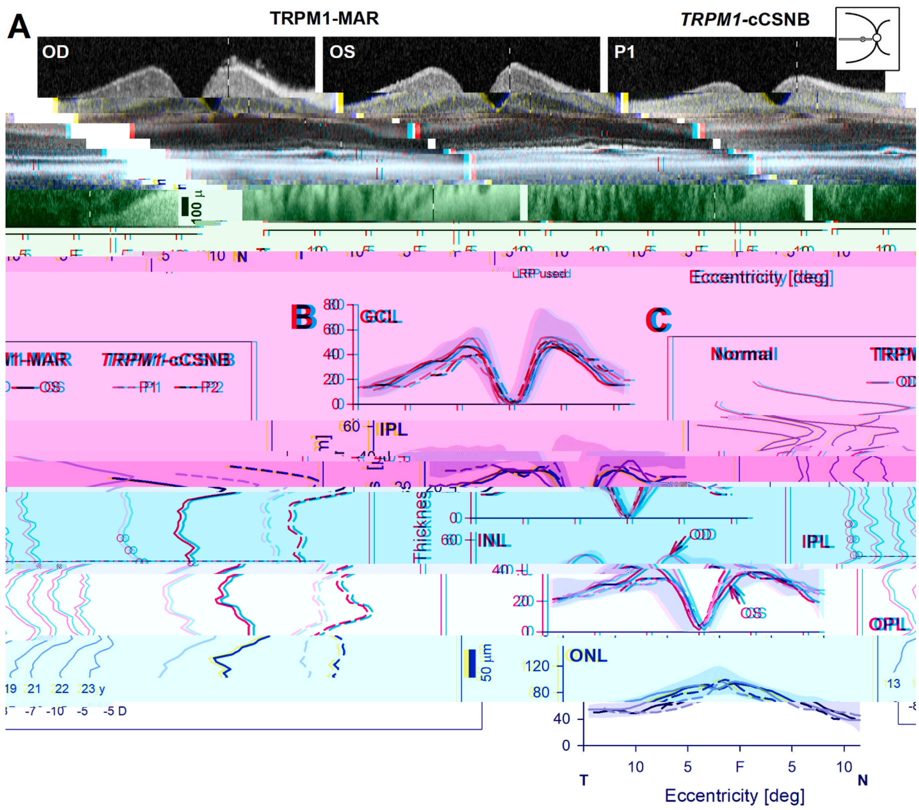

Fig. 2. **A.** Cross sectional SD-OCT image along horizontal meridian through the fovea of the right (OD) and left eye (OS) in the TRPM1-MAR patient. The OS image is flipped horizontally and presented in the same orientation as the OD to facilitate comparisons with the *TRPM1*-cCSNB patient. Vertical dashed lines point to location used for analyses in (C). **B.** Ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL) and outer nuclear layer (ONL) thicknesses as function of eccentricity in each eye of the patient (OD, *dark gray line*; OS, *black line*), compared with normal limits (normal mean ±2SD, *light gray band*). Diagonal arrows points to a location where the INL of the affected and contralateral eye of the patient with TRPM1-MAR departed from each other. Dashed lines represent the data from two patients with *TRPM1*-cCSNB. **C.** Longitudinal reflectivity profiles (LRPs) extracted from a location 4° in nasal retina (*vertical dashed lines* in A) are used to investigate possible differences in the structural details between the two eyes of the patient with, TRPM1-MAR and compare to the LRPs from the patients with *TRPM1*-cCSNB. The inner (IPL) and outer plexiform layer (OPL) are labeled to the left of representative LRPs from otherwise normal myopic eyes spanning the range of ages and refractive errors (annotated at the *bottom of traces*) that may be expected in *TRPM1*-cCSNB. The normal pentalaminar structure of the histologic IPL correspond to three small signal peaks (*circles overlapping first LRP*) interspaced by two troughs illustrated in three normal subjects (*thin gray lines*) and in the right eye of the patient (*dark gray line*). LRPs are aligned by the deepest of the three IPL peaks (*horizontal dashed line*). The affected eye of the patient with MAR (*black* LRP) shows only two IPL peaks. Similar findings are seeing in the patients with *TRPM1*-cCSNB (*dashed LRPs*). T, temporal, N, nasal retina.

the earliest appointment was normal in the right eye and there was a depression of central sensitivities in the left eye (Fig. 3B). Microperimetry three months after Nivolumab discontinuation demonstrated significant improvement of retinal sensitivities in the left eye and continued normal sensitivities in the right eye (Fig. 3B). Given that our patient continued to improve in subjective symptoms, ERG and psychophysical testing, the decision was made to continue withholding nivolumab and closely monitor her without administering immunosuppression. There were no obvious structural changes on the LRP signals post-discontinuation using identical LRP analyses (data not shown), consistent with the incomplete recovery of the inner retinal dysfunction by ERGs.

. iscussion

This study describes a patient with a unilateral presentation of MAR associated with anti-TRMP1 AAbs possibly triggered by immunotherapy with Nivolumab used to consolidate cancer remission. The unusual unilateral manifestation offered a unique opportunity to explore mechanisms of disease in this form of acquired inner retinal dysfunction, thus going beyond the presentation of an infrequent case. The classical inner retinal dysfunction documented with electroretinography in the affected eye of the patient was associated with severe loss of rod-mediated sensitivities within the central retina, confirming a single earlier observation in MAR.[6] The sensitivity losses showed a predilection for the central and infero-nasal pericentral retina as determined with microperimetry, reminiscent of what has been rarely reported in other autoimmune retinopathies, including CAR, MAR and other paraneoplastic retinopathies.[6,45–54] The source for this topographical predilection, which appears to be independent on whether the main changes are in the outer or the inner retina, is unclear, but may relate to greater exposure of the peripapillary and central retina to autoantigens originating from the rich retinal and choroidal vasculature of the region. A similar predilection for the peripapillary and central retina has been repeatedly reported in retinopathies with suspected inflammatory or immune etiology, including forms of acute zonal occult outer retinopathy and multiple evanescent white dot syndrome.[12,17,51,55–58]

Although the retina appeared normally laminated on cross-sectional imaging with SD-OCT, careful inspection using LRP analyses revealed unexpected changes. The GCL and INL were thinner in the affected eye compared to the control. Importantly, the IPL was abnormal. Instead of the pentalaminar architecture of the normal IPL, there were only two peaks in the IPL LRP profile. The abnormality, while somewhat unanticipated, relates well with both the inner retinal dysfunction along the ON-BPC pathway and with the role of TRPM1 in the synaptic transmission along this pathway, as well as with the localization of the protein in ON-BPC and of the immunostaining at the IPL and OPL against TRMP1 epitopes involved in MAR.[10,19–28,59] TRPM1 is found in

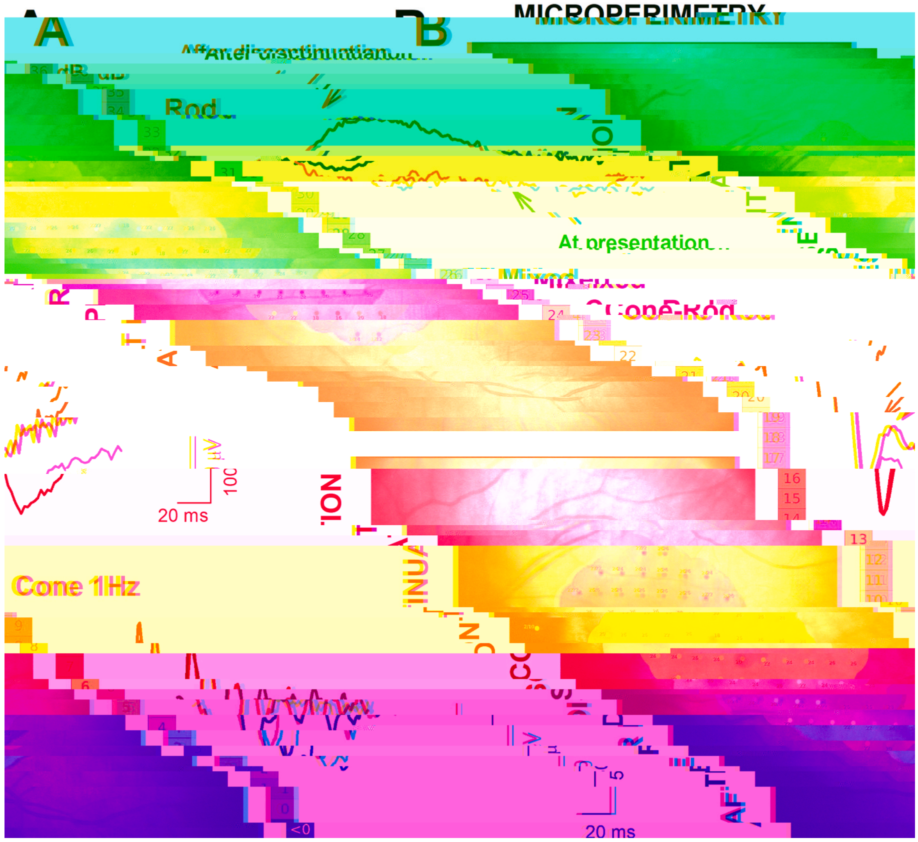

Fig. . A. Full-field ERGs demonstrating inner retinal functional improvement in the affected eye of the TRPM1-MAR patient by comparing ERGs at presentation (*red* waveforms) and the about seven months after nivolumab cessation (*black* waveforms). Rod responses are clearly detectable after discontinuation and there is improvement of the inner retinal signal in the mixed cone-rod responses (diagonal arrow) as well as in the 1Hz cone response with return of a normal morphology of the waveform for the LA 1Hz cone response from the square shaped a-awve at baseline. **B.** Fundus tracked perimetric (microperimetry) sensitivities plotted to a colored scale (*right*) demonstrating reduced foveal and perifoveal sensitivities on baseline examination and improved sensitivities on repeat testing three months after Nivolumab cessation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

melanocytes, though why it may be targeted by the immune system in melanoma patients is poorly understood.[3,10,11,17,19,20,22,60,61] One theory proposes that aberrant splicing of the TRPM1 mRNA in malignant melanocytes may result in neo-antigens that trigger an immune response, with main targets in the synaptic terminals.[20,22]

The functional phenotype in TRPM1-associated MAR is remarkably similar to that of patients with cCSNB caused by mutations in the gene that encodes this channel protein.[6,29] Analogous to the functional comparisons between MAR and CSNB performed in the past, we compared the structural phenotypes of MAR and cCSNB that caused by pathogenic variants in *TRPM1*. The overall goal was to compare different mechanisms of disease that converge on a common downstream target. Commonalities of the structural and functional phenotype may help interpret and validate nonspecific positive autoimmune panel results in cases that are not obviously MAR, CAR or non-paraneoplastic AIRs. Somewhat unexpectedly we found nearly identical subtle abnormalities at the level of the GCL, INL and IPL, adding support to structural abnormalities reported in *TRPM1*-cCNSB and reminiscent of the changes described in a mouse model of pAIR induced by autoantibodies against TRPM1.[62–64] It is unclear why there is an apparent predilection for the synaptic end at the IPL, instead of the more studied OPL. Abnormalities at the level of the OPL, with less defined structural features on OCT, may be more difficult to discern. It is also perhaps relevant to note the association with hypoplastic nerves and thin GCL in this and in a previous report as they point to a common mechanistic denominator.[63] AIRs caused by different AAbs, including those associated with ON-BPC dysfunction, often present with ill-defined, often overlapping phenotypes. Predilection of certain abnormalities in MAR and other AAbs illustrated in the current report, may help the frequently elusive diagnosis of these conditions. Descriptions in larger number of both MAR and *TRPM1*-CSNB patients in a similar manner are needed to clarify the significance of our findings.

Over the past decade, checkpoint inhibitors (CPI) have become a promising new addition to the oncologist's armamentarium for addressing treatment of melanoma and other tumors. These immunomodulatory medications target certain ligands that cancerous cells express to evade the body's natural immunity. They include programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which inhibit the activity of T lymphocytes when bound to the corresponding receptors on the immune cell surface. CPIs bind both the receptor and the ligand to prevent cancer cells from employing these dampening effects on the immune system, thereby unleashing the body's natural defense.[65] While this class of medications has shown great promise, they have been associated with a variety of immune-related side effects involving virtually any organ system.[66] Immune-related adverse events have been shown to occur in up to 70 % of patients receiving anti–PD-1 agents and in up to 90 % of patients receiving anti–CTLA 4 medications.[67] While ocular side effects are uncommon, with an estimated prevalence of one percent of all treated patients,[31] there have been reports of various manifestations including, but not limited to: Vogt-Koyanagi-Harada syndrome, exudative retinal detachment, central retinal artery occlusion, optic neuropathy, orbital myopathy, orbital apex syndrome, scleritis, periocular edema, and anterior, posterior and panuveitis.[68–70] PD-1 and CTLA-4 inhibitors have been implicated in the development AIR. While several reports have described the onset of MAR in those treated with checkpoint inhibitors,[71] only a few have demonstrated a temporal relationship between MAR symptoms and CPI initiation or resolution of the retinopathy upon discontinuation, ideal factors to support causality. The time course followed in our case after discontinuation of the medication adds support to the role of this type of medication in ocular autoimmunity.

Dolaghan et al. described a patient with metastatic melanoma who developed an array of immune-related adverse effects including anterior uveitis, colitis, adrenal insufficiency, and diabetes after being treated with two cycles of Ipilimumab/Nivolumab and five cycles of Pembrolizumab.[72] After the resolution of his uveitis with CPI discontinuation, he his poor vision led to a diagnosis of MAR with AAbs against recoverin and carbonic anhydrase II. Shahzad et al. reported on a patient with metastatic uveal melanoma who began developing symptoms and inner retinal dysfunction consistent with MAR three weeks after initiation with ipilimumab and nivolumab.[73] After courses of oral and intravitreal steroids the patient ultimately improved with minor residual vision loss. Elwood et al. described a woman with metastatic melanoma who presented with visual field loss and photopsias four months after four cycles of ipilimumab/nivolumab.[74] MAR was diagnosed based on ERG and AAbsagainst 60-kDa protein. The visual symptoms worsen over 14 months despite the cessation of therapy due to side effects. The patient improved over the ensuing ten months. Lastly, Kim et al. reported on a patient with metastatic cutaneous melanoma who developed floaters and photopsias after one cycle of ipilimumab and nivolumab.[75] ERGs and AAbswere consistent with MAR. She also developed transaminitis and hypopituitarism. Immunotherapy was discontinued and she was treated with high dose IV steroids followed by intravenous immunoglobulin. At ten-month follow up, her visual acuity was 20/20. The time course of our case adds support to the role of these agents as triggers of retinal autoimmune events. The patient was visually asymptomatic for over a year after the diagnosis of melanoma, became symptomatic three months after starting Nivolumab with her last cycle occurring one week after the onset of her symptoms. Her symptoms and vision improved confirmed by psychophysics and electroretinography two months after therapy cessation without the help of immunosuppression. The symptomatic improvement was not accompanied by total resolution of the functional abnormalities as substantial ON-BPC dysfunction was still documented by ERGs months after discontinuation of the medication. The source of this residual loss may relate to potentially irreversible structural synaptic changes, some of which were documented by OCT in the current report. OCTs have proven useful as a monitoring tool in the treatment of advance cutaneous melanoma.[76] The role that this clinically available, non-invasive technique may have to monitor the retinal impact of immunotherapies for advanced melanoma before the onset of visual symptoms may warrant further study.

CAR and MAR are typically or become bilateral within a short time after presentation, though there have been case reports of unilateral disease despite extended follow-up periods.[8,16] Reddy et al. described a patient with stage IV lung adenocarcinoma who developed AIR attributed to nivolumab therapy.[77] The patient's symptoms were bilateral and OCT and FAF demonstrated changes in both eyes, however, the ERG was normal in the left eye. Almeida et al. reported on a patient with squamous cell carcinoma who underwent resection without adjuvant treatment and presented 11 years later with subjective concerns and OCT, Goldmann visual field and ERG findings consistent with AIR of only the right eye with the left eye remaining unaffected during 3 years of follow up.[78] Javaid et al. described a patient with cervical intraepithelial neoplasia who presented with unilateral right eye symptoms with multi-modal imaging and ERG confirming rod and cone degeneration compared to the left, which was normal.[79] Roels et al. described a patient who presented with six weeks of progressive photopsias, photophobia and a central scotoma in the right eye and a unilateral electronegative ERGs.[80] Imaging detected adenocarcinoma of the right ovary. She ultimately tested positive for serum autoantibodies against TRPM1, confirming the diagnosis. After surgical resection and treatment with Rituximab and corticosteroids, she experienced progressive improvement in symptoms and the ERG normalized. Janaky et al. described a patient with a cutaneous malignant melanoma and unilateral right eye symptoms with an electronegative ERG.[81] Like our case, ERGs remained normal in the contralateral eye over time. The patient's serum displayed strong binding to retinal bipolar cells, suggestive, like in our case, the possibility of unilateral MAR. The reason why patients with AIR show uniocular manifestations remain unclear, but suggests an eye-specific susceptibility to the autoimmune attack.[82,83]

While the checkpoint inhibitors have revolutionized the treatment of otherwise recalcitrant metastatic disease, there is mounting evidence that they may cause significant immune-related side effects, which can be visually significant. Symptoms and multimodal imaging findings of autoimmune retinopathy are often subtle and may be misdiagnosed. The ophthalmologist must remain cognizant of the possibility of a paraneoplastic process in patients with underlying malignancy, especially those receiving immunomodulatory medications.

. Conc usions

This case of unilateral MAR triggered by immunotherapy with documented partial functional recovery after discontinuation of the medication adds support to the role of this type of medication in ocular autoimmunity. Comparisons between the affected and unaffected eye in this unilateral MAR case revealed inner retinal abnormalities and abnormal lamination of the IPL associated with the classical retina-wide ON-BPC dysfunction by electroretinography, and localized central rod-mediated sensitivity losses by two-color dark-adapted perimetry. A nearly identical structural phenotype in two cases of *TRPM1*-cCSNB and a case of anti-TRPM1 positive MAR supports a specific structuraland functional phenotype caused by diverse mechanisms converging on TRPM1 as the common downstream target. Further studies are warranted to stablish the role of this detailed phenotype as additional confirmatory evidence for the diagnosis and management

& editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Appendi A. upp e entar data

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e erences

1. Alexander KR, Fishman GA, Peachey NS, Marchese AL, Tso MO. 'On' response defect in paraneoplastic night blindness with cutaneous malignant melanoma. *Invest Ophthalmol Vis Sci*. 1992;33:477–483.
2. Milam A, Dacey D, Dizhoor A. Recoverin immunoreactivity in mammalian cone bipolar cells. *Vis Neurosci*. 1993;10:1–12.
3. Adamus G. Autoantibody targets and their cancer relationship in the pathogenicity of paraneoplastic retinopathy. *Autoimmun Rev*. 2009;8:410–414.
4. Gass J. *Acute Vogt-Koyanagi-Harada-like syndrome occurring in a patient with metastatic cutaneous melanoma. Uveitis Update: Proceedings of the First International Symposium on Uveitis*. Amsterdam: Elsevier Science; 1984:407–408.
5. Ng CC, Alsberge JB, Qian Y, Freund KB, Cunningham ETJ. Vogt–Koyanagi–Harada-like uveitis followed by melanoma-associated retinopathy with foveal chorioretinal atrophy and choroidal neoveascularizatio in a patient with metastatic cutaneous melanoma. 2023;17:18–22.
6. Milam AH, Saari JC, Jacobson SG, Lubinski WP, Feun LG, Alexander KR. Autoantibodies against retinal bipolar cells in cutaneous melanoma-associated retinopathy. *Invest Ophthalmol Vis Sci*. 1993;34:91–100.
7. Berson EL, Lessell S. Paraneoplastic night blindness with malignant melanoma. *Am J Ophthalmol*. 1988;106:307–311.
8. Keltner JL, Thirkill CE, Yip PT. Clinical and immunologic characteristics of melanoma-associated retinopathy syndrome: eleven new cases and a review of 51 previously published cases. *J Neuro Ophthalmol*. 2001;21:173–187.
9. Ripps H, Carr RE, Siegel IM, Greenstein VC. Functional abnormalities in vincristine-induced night blindness. *Investigative Ophthalmology Visual Science*. 1984;25:787–794.
10. Varin J, Reynolds MM, Bouzidi N, et al. Identification and characterization of novel TRPM1 autoantibodies from serum of patients with melanoma-associated retinopathy. *PLoS One*. 2020;15, e0231750.
11. Ueno S, Ito Y, Maruko R, Kondo M, Terasaki H. Choroidal atrophy in a patient with paraneoplastic retinopathy and anti-TRPM1 antibody. *Clin Ophthalmol*. 2014;8:369–373.
12. Ueno S, Inooka D, Nakanishi A, et al. Clinical course of paraneoplastic retinopathy with anti-TRPM1 autoantibody in Japanese cohort. 2019;39:2410–2418.
13. Shinohara Y, Mukai R, Ueno S, Akiyama H. Clinical findings of melanoma-associated retinopathy with anti-TRPM1 antibody. *Case Reports in Ophthalmological Medicine*. 2021;2021:1–5.
14. Lei B, Bush RA, Milam AH, Sieving PA. Human melanoma-associated retinopathy (MAR) antibodies alter the retinal ON-response of the monkey ERG in vivo. *Invest Ophthalmol Vis Sci*. 2000;41:262–266.
15. Goetgebuer G, Kestelyn-Stevens AM, De Laey JJ, Kestelyn P, Leroy BP. Cancer-associated retinopathy (CAR) with electronegative ERG: a case report. *Doc Ophthalmol*. 2008;116:49–55.
16. Carboni G, Forma G, Bond AD, Adamus G, Iannaccone A. Bilateral paraneoplastic optic neuropathy and unilateral retinal compromise in association with prostate cancer: a differential diagnostic challenge in a patient with unexplained visual loss. *Doc Ophthalmol*. 2012;125:63–70.
17. Ueno S, Nakanishi A, Nishi K, Suzuki S, Terasaki H. Case of paraneoplastic retinopathy with retinal ON-bipolar cell dysfunction and subsequent resolution of ERGs. *Doc Ophthalmol*. 2015;130:71–76.
18. Lu Y, Jia L, He S, et al. Melanoma-associated retinopathy: a paraneoplastic autoimmune complication. *Arch Ophthalmol*. 2009;127:1572–1580.
19. Kondo M, Sanuki R, Ueno S, et al. Identification of autoantibodies against TRPM1 in patients with paraneoplastic retinopathy associated with ON bipolar cell dysfunction. *PLoS One*. 2011;6, e19911.
20. Dhingra A, Fina ME, Neinstein A, et al. Autoantibodies in melanoma-associated retinopathy target TRPM1 cation channels of retinal ON bipolar cells. *J Neurosci*. 2011;31:3962–3967.
21. Duvoisin RM, Haley TL, Ren G, Strycharska-Orczyk I, Bonaparte JP, Morgans CW. Autoantibodies in melanoma-associated retinopathy recognize an epitope conserved between TRPM1 and TRPM3. *Investigative Opthalmology Visual Science*. 2017;58:2732.
22. Duvoisin RM, Ren G, Haley TL, Taylor MH, Morgans CW. TRPM1 autoantibodies in melanoma patients without self-reported visual symptoms. *Invest Ophthalmol Vis Sci*. 2019;60:2330–2335.
23. Xiong W-H, Duvoisin RM, Adamus G, Jeffrey BG, Gellman C, Morgans CW. Serum TRPM1 autoantibodies from melanoma associated retinopathy patients enter retinal ON-bipolar cells and attenuate the electroretinogram in mice. *PLoS One*. 2013;8, e69506.
24. Morgans CW, Brown RL, Duvoisin RM. TRPM1: the endpoint of the mGluR6 signal transduction cascade in retinal ON-bipolar cells. *Bioessays*. 2010;32:609–614.
25. Koike C, Obara T, Uriu Y, et al. TRPM1 is a component of the retinal ON bipolar cell transduction channel in the mGluR6 cascade. *Proc Natl Acad Sci USA*. 2010;107:332–337.
26. Agosto MA, Anastassov IA, Wensel TG. Differential epitope masking reveals synapse-specific complexes of TRPM1. *Vis Neurosci*. 2018;35.
27. Agosto MA, Adeosun AAR, Kumar N, Wensel TG. The mGluR6 ligand-binding domain, but not the C-terminal domain, is required for synaptic localization in retinal ON-bipolar cells. *J Biol Chem*. 2021;297, 101418.
28. Koike C, Numata T, Ueda H, Mori Y, Furukawa T. TRPM1: a vertebrate TRP channel responsible for retinal ON bipolar function. *Cell Calcium*. 2010;48:95–101.
29. Audo I, Kohl S, Leroy BP, et al. TRPM1 is mutated in patients with autosomal-recessive complete congenital stationary night blindness. *Am J Hum Genet*. 2009;85:720–729.
30. Antoun J, Titah C, Cochereau I. Ocular and orbital side-effects of checkpoint inhibitors. *a review article*. 2016;28:288–294.
31. Dalvin LA, Shields CL, Orloff M, Sato T, Shields JA. Checkpoint inhibitor immune therapy: systemic indications and ophthalmic side effects. *Retina*. 2018;38:1063–1078.
32. Robson AG, Frishman LJ, Grigg J, et al. ISCEV Standard for full-field clinical electroretinography (2022 update). *Doc Ophthalmol*. 2022;144:165–177.
33. Jacobson SG, Voigt WJ, Parel JM, et al. Automated light- and dark-adapted perimetry for evaluating retinitis pigmentosa. *Ophthalmology*. 1986;93:1604–1611.
34. Remulla JFC. Cutaneous melanoma-associated retinopathy with retinal periphlebitis. *Arch Ophthalmol*. 1995;113:854.
35. Murayama K, Takita H, Kiyohara Y, Shimizu Y, Tsuchida T, Yoneya S. [Melanoma-associated retinopathy with unknown primary site in a Japanese woman]. *Nippon Ganka Gakkai Zasshi*. 2006;110:211–217.
36. Anastasakis A, Dick AD, Damato EM, Spry PG, Majid MA. Cancer-associated retinopathy presenting as retinal vasculitis with a negative ERG suggestive of on-bipolar cell pathway dysfunction. *Doc Ophthalmol*. 2011;123:59–63.
37. Tanna H, Dubis AM, Ayub N, et al. Retinal imaging using commercial broadband optical coherence tomography. *Br J Ophthalmol*. 2010;94:372–376.
38. Zhang T, Kho AM, Srinivasan VJ. Improving visible light OCT of the human retina with rapid spectral shaping and axial tracking. *Biomed Opt Express*. 2019;10:2918–2931.
39. Miller DT, Kurokawa K. Cellular-scale imaging of transparent retinal structures and processes using adaptive optics optical coherence tomography. *Annual Review of Vision Science*. 2020;6:115–148.
40. Zhang T, Kho AM, Srinivasan VJ. In vivo morphometry of inner plexiform layer (IPL) stratification in the human retina with visible light optical coherence tomography. *Front Cell Neurosci*. 2021;15, 655096.
41. Ghassabi Z, Kuranov RV, Schuman JS, et al. In vivo sublayer analysis of human retinal inner plexiform layer obtained by visible-light optical coherence tomography. *Investigative Opthalmology Visual Science*. 2022;63:18.
42. Wang MM, Janz R, Belizaire R, Frishman LJ, Sherry DM. Differential distribution and developmental expression of synaptic vesicle protein 2 isoforms in the mouse retina. *J Comp Neurol*. 2003;460:106–122.
43. Simunovic MP, Moore AT, Maclaren RE. Selective automated perimetry under photopic, mesopic, and scotopic conditions: detection mechanisms and testing strategies. *Translational Vision Science Technology*. 2016;5:10.
44. Taylor LJ, Josan AS, Pfau M, Simunovic MP, Jolly JK. Scotopic microperimetry: evolution, applications and future directions. *Clin Exp Optom*. 2022;105:793–800.
45. Dabir S, Mangalesh S, Govindraj I, Mallipatna A, Battu R, Shetty R. Melanoma associated retinopathy: a new dimension using adaptive optics. *Oman J Ophthalmol*. 2015;8:125–127.
46. Lima LH, Greenberg JP, Greenstein VC, et al. Hyperautofluorescent ring in autoimmune retinopathy. *Retina*. 2012;32:1385–1394.
47. Chen FK, Chew AL, Zhang D, et al. Acute progressive paravascular placoid neuroretinopathy with negative-type electroretinography in paraneoplastic retinopathy. *Doc Ophthalmol*. 2017;134:227–235.
48. Chaves LJ, Albuquerque ML, Schnorr A, et al. A slow-release dexamethasone implant for cancer-associated retinopathy. *Arq Bras Oftalmol*. 2023;86:171–174.
49. Hwang CK, Kolomeyer AM, Brucker AJ, Morgan JIW, Nichols CW, Aleman TS. Localized bilateral juxtafoveal photoreceptor loss in poems: a new association. *Retina*. 2017;37:e91–e92.
50. Miller CG, Brucker AJ, Perry LM, et al. Outer Retinopathy and Microangiopathy in Acute Myelogenous Leukemia. vol. 9900;10.1097/ICB.0000000000001294.
51. Stanwyck LK, Place EM, Comander J, Huckfeldt RM, Sobrin L. Predictive value of genetic testing for inherited retinal diseases in patients with suspected atypical autoimmune retinopathy. *Am J Ophthalmol Case Rep*. 2019;15, 100461.
52. Sarkar P, Mehtani A, Gandhi HC, Bhalla JS, Tapariya S. Paraneoplastic ocular syndrome: a pandora's box of underlying malignancies. *Eye*. 2022;36:1355–1367.
53. Bourgault S, Baril C, Vincent A, et al. Retinal degeneration in autoimmune polyglandular syndrome type 1: a case series. *Br J Ophthalmol*. 2015;99:1536–1542.
54. Culp CJ, Pappas CM, Toso M, Qu P, Mamalis N, Hageman GS. Clinical, histological and genetic findings in a donor with a clinical history of type 1 Autoimmune

Polyendocrinopathy Syndrome. *American Journal of Ophthalmology Case Reports*. 2022;25, 101266.
55. Shen C-H, Hsieh C-C, Jiang K-Y, et al. AUY922 induces retinal toxicity through attenuating TRPM1. *J Biomed Sci*. 2021;28.
56. Sandhu HS, Kolomeyer AM, Lau MK, et al. Acute exudative paraneoplastic polymorphous vitelliform maculopathy during vemurafenib and pembrolizumab treatment for metastatic melanoma. *Retin Cases Brief Rep*. 2019;13:103–107.
57. Essilfie J, Bacci T, Abdelhakim AH, et al. *ARE THERE TWO FORMS OF MULTIPLE EVANESCENT WHITE DOT SYNDROME?*. vol. 42. 2022:227–235.
58. Serrar Y, Cahuzac A, Gascon P, et al. Comparison of primary and secondary forms of multiple evanescent white dot. *SYNDROME*. 2022;42:2368–2378.
59. Morgans CW, Bayley PR, Oesch NW, Ren G, Akileswaran L, Taylor WR. Photoreceptor calcium channels: insight from night blindness. *Vis Neurosci*. 2005;22: 561–568.
60. Gyoten D, Ueno S, Okado S, et al. Broad locations of antigenic regions for anti-TRPM1 autoantibodies in paraneoplastic retinopathy with retinal ON bipolar cell dysfunction. *Exp Eye Res*. 2021;212, 108770.
61. Dalal MD, Morgans CW, Duvoisin RM, et al. Diagnosis of occult melanoma using transient receptor potential melastatin 1 (TRPM1) autoantibody testing. *Ophthalmology*. 2013;120:2560–2564.
62. Al-Hujaili H, Taskintuna I, Neuhaus C, Bergmann C, Schatz P. Long-term follow-up of retinal function and structure in TRPM1-associated complete congenital stationary night blindness. *Mol Vis*. 2019;25:851–858.
63. Al Oreany AA, Al Hadlaq A, Schatz P. Congenital stationary night blindness with hypoplastic discs, negative electroretinogram and thinning of the inner nuclear layer. *Graefes Arch Clin Exp Ophthalmol*. 2016;254:1951–1956.
64. Ueno S, Nishiguchi KM, Tanioka H, et al. Degeneration of retinal on bipolar cells induced by serum including autoantibody against TRPM1 in mouse model of paraneoplastic retinopathy. *PLoS One*. 2013;8, e81507.
65. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12:252–264.
66. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2016;27:1362.
67. Kostine M, Chiche L, Lazaro E, et al. Opportunistic autoimmunity secondary to cancer immunotherapy (OASI): an emerging challenge. *Rev Med Interne*. 2017;38: 513–525.
68. Young L, Finnigan S, Streicher H, et al. Ocular adverse events in PD-1 and PD-L1 inhibitors. *Journal for ImmunoTherapy of Cancer*. 2021;9, e002119.
69. Heng JS, Kim JM, Jones DK, et al. Autoimmune retinopathy with associated anti-retinal antibodies as a potential immune-related adverse event associated with immunotherapy in patients with advanced cutaneous melanoma: case series and systematic review. *BMJ Open Ophthalmology*. 2022;7, e000889.
70. Liu CY, Francis JH, Brodie SE, et al. Retinal toxicities of cancer therapy drugs: biologics, small molecule inhibitors, and chemotherapies. *Retina*. 2014;34: 1261–1280.
71. Casselman P, Jacob J, Schauwvlieghe P-P. Relation between ocular paraneoplastic syndromes and Immune Checkpoint Inhibitors (ICI): review of literature. *Journal of Ophthalmic Inflammation and Infection*. 2023;13.
72. Dolaghan MJ, Oladipo B, Cooke CA, McAvoy CE. Metastatic melanoma and immunotherapy-related uveitis: an incidence in Northern Ireland. *Eye*. 2019;33: 1670–1672.
73. Shahzad O, Thompson N, Clare G, Welsh S, Damato E, Corrie P. Ocular adverse events associated with immune checkpoint inhibitors: a novel multidisciplinary management algorithm. *Therapeutic Advances in Medical Oncology*. 2021;13, 175883592199298.
74. Elwood KF, Pulido JS, Ghafoori SD, Harper CA, Wong RW. Choroidal neovascularization and chorioretinal atrophy in a patient with melanoma-associated retinopathy after ipilimumab/nivolumab combination therapy. *Retin Cases Brief Rep*. 2021;15:514–518.
75. Kim JM, Materin MA, Sznol M, et al. Ophthalmic immune-related adverse events of immunotherapy: a single-site case series. *Ophthalmology*. 2019;126:1058–1062.
76. Nti AA, Serrano LW, Sandhu HS, et al. Frequent subclinical macular changes in combined BRAF/MEKinhibition with high-dose hydroxychloroquine as treatment for advanced BRAF mutant melanoma: preliminary results from a phase I/II clinical treatment trial. *Retina*. 2018. https://doi.org/10.1097/IAE.0000000000002027. ; [Epub ahead of print] Jan 10, 2018.
77. Reddy M, Chen JJ, Kalevar A, Terribilini R, Agarwal A. Immune retinopathy associated with nivolumab administration for metastatic non-small cell lung cancer. *Retin Cases Brief Rep*. 2020;14:120–126.
78. Almeida DR, Chin EK, Niles P, Kardon R, Sohn EH. Unilateral manifestation of autoimmune retinopathy. *Can J Ophthalmol*. 2014;49:e85–e87.
79. Javaid Z, Rehan SM, Al-Bermani A, Payne G. Unilateral cancer-associated retinopathy: a case report. *Scott Med J*. 2016;61:155–159.
80. Roels D, Ueno S, Talianu CD, Draganova D, Kondo M, Leroy BP. Unilateral cancer-associated retinopathy: diagnosis, serology and treatment. *Doc Ophthalmol*. 2017; 135:233–240.
81. Janaky M, Palffy A, Kolozsvari L, Benedek G. Unilateral manifestation of melanoma-associated retinopathy. *Arch Ophthalmol*. 2002;120:866–867.
82. Reddy S, Finger PT. Unilateral diffuse uveal melanocytic proliferation (DUMP). *Br J Ophthalmol*. 2007;91:1726–1727.
83. Spaide RF. Unilateral diffuse uveal melanocytic proliferation. *Retin Cases Brief Rep*. 2018;12:263–265.