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A seven-year electroretinography follow-up of a patient with melanoma-associated retinopathy stabilized on pembrolizumab treatment☆

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ABSTRACT

Purpose: Melanoma-associated retinopathy (MAR) is a rare, auto-immune paraneoplastic syndrome associated with metastatic melanoma. Over the last decade, patient survival has improved dramatically, mainly due to the development of immunotherapy. However, data on long-term MAR patient follow-up and response to modern standard-of-care treatment are lacking. This single-patient case report presents a seven-year, multimodal follow-up of a young MAR patient treated with immune-checkpoint inhibitors.

Observations: A 46-year-old Israeli male with a history of cutaneous malignant melanoma presented with sudden onset of bilateral shimmering, flickering, and nyctalopia a year and a half after diagnosis. Shortly thereafter, new subcarinal metastasis was observed on Positron Emission Tomography–Computed Tomography. Significantly reduced electroretinography (ERG) a- and b-wave responses led to a diagnosis of MAR, later confirmed by high titers of autoantibodies against retinal bipolar cells. Half a year later, macular thinning, particularly within the inner nuclear and inner plexiform layers of the outer macular ring, with no substantial change in the outer retina, was observed on optical coherence tomography (OCT). A treatment regimen combining intravenous immune globulin, azathioprine, and prednisone allowed partial steroid tapering over the following 2.5 years but showed substantial toxicity and a lack of significant improvement on OCT and ERG. Pembrolizumab treatment was initiated following metastatic progression and resulted in stabilization of the patient's primary oncologic disease, as well as an increase in macular thickness and enhanced retinal function with an increase of over 60 % in dark adapted (DA) b-wave response over the following year.

Conclusions and importance: MAR may be the first sign of systemic metastatic melanoma, thus warranting a high degree of clinical suspicion. While OCT and ERG showed mostly concordant results over the patient's follow-up, ERG proved to be a more sensitive tool for the early diagnosis of MAR. Early immunotherapy treatment should be considered in antibody-positive MAR patients.

1. Introduction

Melanoma-associated retinopathy (MAR) is a rare paraneoplastic syndrome caused by heterogeneous anti-tumor antibodies, which most often cross-react with bipolar cells of rod photoreceptors and their axons. These antibodies, such as the anti-transient receptor potential cation channel, subfamily M, member 1 (TRPM1) antibody, lead to disruption of the synaptic transmission and eventually cell degeneration.[1,2] This results in predominantly rod-related visual symptoms, such as sudden onset of shimmering, flickering, or pulsating photopsias and decreased night vision (nyctalopia).[3]

In most MAR cases, fundus appearance, visual acuity (VA), central

☆ Claims of Priority: After conducting a literature review on 01.08.2024 utilizing PubMed, Google Scholar, and EMBASE using the key words (Melanoma associated retinopathy; MAR), we did not find any prior reports of long-term, detailed multimodal follow-up of MAR patients.

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visual field (VF), and color vision remain normal. In more advanced cases, painless, progressive loss of VA and VF, sometimes accompanied by optic disc pallor, retinal vessel attenuation, and areas of retinal pigment epithelium (RPE) atrophy, may occur.[3] Retinal architecture and thickness may also appear normal on optical coherence tomography (OCT) in the early stages of the disease, with inner retinal thinning as the disease progresses.[4] Patients with MAR typically present with reduced dark-adapted electroretinography (ERG) b-waves and normal a-waves, suggesting compromised bipolar cell function.[3]

Two major treatment strategies for MAR include immunosuppression

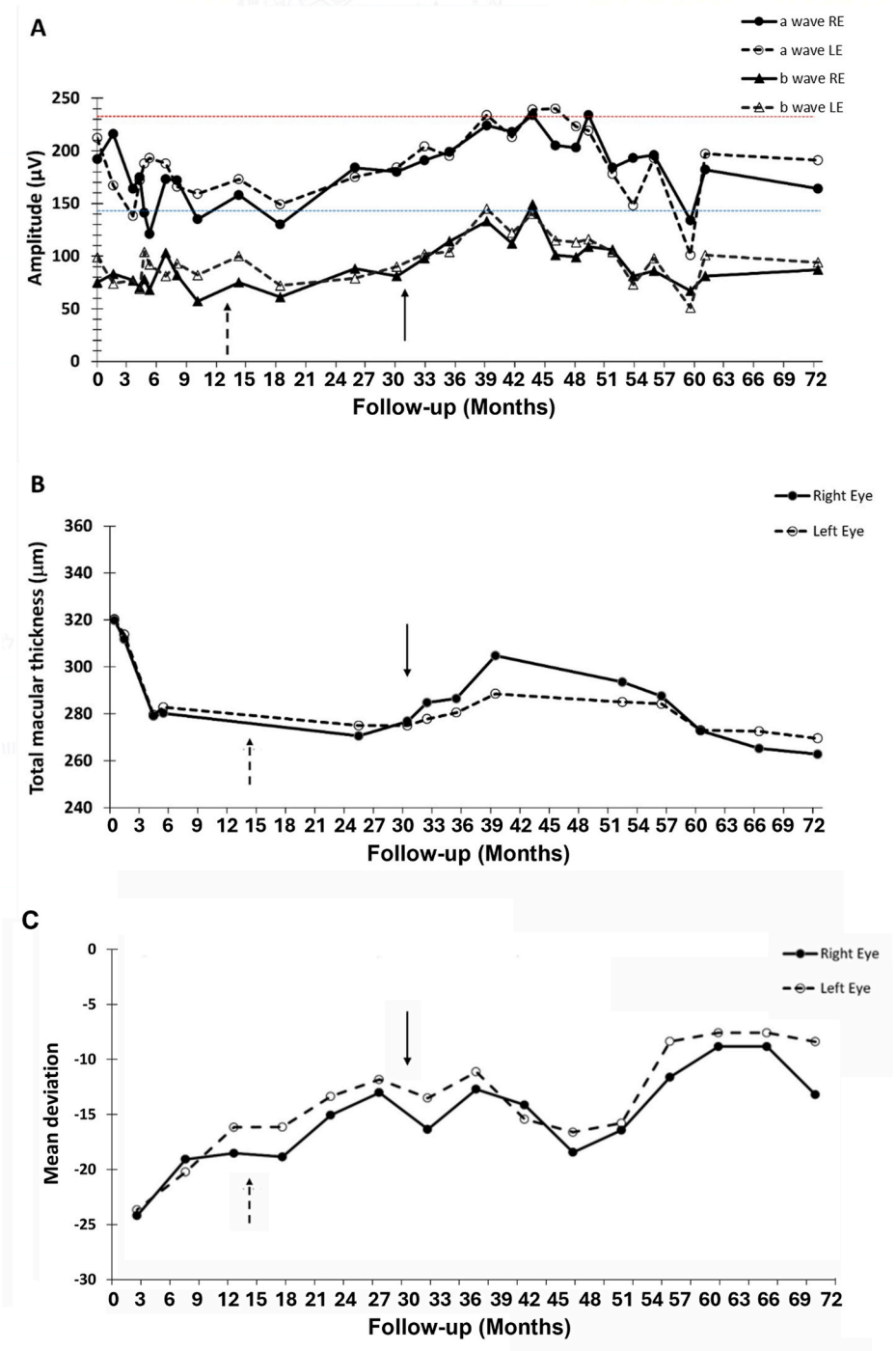

Fig. 1. A- Full-field ERG a- (circles) and b-wave (triangles) amplitudes over seven years in the patient's right (closed shapes) and left (open shapes) eye. While the DA 10.0 a-wave amplitude remained mainly within the normal amplitude range (>145μV, highlighted with a horizontal dashed blue line), the DA 10.0 b-wave amplitudes were substantially reduced on presentation and throughout the follow-up (<235 μV),[15] but showed substantial improvement following pembrolizumab treatment (black arrow). The horizontal red dashed line indicates the minimal normal b-wave for the patient's age group.[8] **B-** Macular OCT total retinal thickness over the same time period in both eyes at the outer macular ring (defined by the EDTRS grid). Similar trends between ERG and OCT measurements were observed throughout the follow-up period, with a delay of approximately six months from disease onset. The dashed-line arrow indicates the initiation of azathioprine and IVIG and the solid arrow indicates the initiation of pembrolizumab treatment. **C-** Visual field (SITA Standard protocol stimulus size III) mean deviation (MD) over the same time period in both eyes, indicating improvement with treatment over time. The dashed arrow indicates the initiation of azathioprine and IVIG and the solid black arrow indicates the initiation of pembrolizumab treatment.

using glucocorticosteroids, immunomodulatory drugs, intravenous immunoglobulin (IVIG), plasma exchange, and control of the underlying malignancy through surgical or non-surgical cytoreduction.[5] This report describes a seven-year multimodal follow-up of a young MAR patient demonstrating substantial improvement following immune-checkpoint inhibitors (ICI) therapy.

2. Case presentation

This case report describes a 46-year-old Israeli man whose medical history included cutaneous melanoma of the upper back (Stage 2: T3N0M0), which was excised fully with wide margins and a clear sentinel lymph node biopsy. Sixteen months later, the patient presented with a sudden onset of visual disturbances, which he described as "static, white, symmetrical circles extending from the superior edges and covering nearly the entire field of vision." He reported no history of ocular complaints besides bilateral myopia (−5.5) nor any family history suggestive of heritable retinal disease. Brain computed tomography and ocular examination, including OCT, showed no significant findings at that time, and he was discharged with a diagnosis of floaters.

The patient's visual symptoms persisted, and Humphrey 24-2 VF testing performed two weeks later showed significant bilateral VF loss in all sectors (MD = −24 in both eyes, Fig. 1C). At this time, the patient's VA, color vision, pupillary light reflex, accommodation, and funduscopic examination were normal. He was, therefore, referred to our department for further testing. Approximately 4 months after symptom onset, an OCT was performed and found normal, despite worsening symptoms that now also included shimmering, flickering photopsia and nyctalopia (Figs. 1B and 2). A full-field ERG following the ISCEV protocol[6] for ERG testing, as previously described by Sher et al.[7] was performed on the same day and showed significant retinal dysfunction, primarily involving rod cells (DA 10.0 cd*s/m^2: a-wave - right eye 192μv, left eye 212μv; b-wave - right eye 75μv, left eye 99μv, Fig. 1A). This ERG showed a severely attenuated DA 0.01 response, while DA 3 and DA 10 demonstrated an electronegative waveform, characterized by a reduced b-wave amplitude with preserved a-wave amplitude (Fig. 3) Prednisone 60 mg/day therapy was initiated.

As part of the patient's routine oncological follow-up, a Positron Emission Tomography–Computed Tomography (PET-CT) scan revealed an active subcarinal lesion. Endoscopic ultrasound (EUS) subsequently confirmed it to be a metastasis. Systemic treatment for melanoma was initiated with dabrafenib and trametinib. Six months after symptom onset, a sample of the patient's blood was sent to the Ocular Immunology Laboratory in Oregon. High titers of autoantibodies against whole retina extract (TRMP1, Recoverin and Guanylate Cyclase-Activating Protein 1) and against optic nerve (neurofilament proteins) were detected. Indirect immunohistochemistry showed strong autoantibody activity against retinal bipolar cells. Together with the ERG results, this solidified the diagnosis of MAR.

The patient's ERG follow-up, shown in Fig. 1A, demonstrated only mild improvement in retinal function following systemic corticosteroid treatment. Of note, during this time, steroid tapering attempts were accompanied by subjective worsening of the patient's nyctalopia, although no clear trend can be established on OCT and ERG. The patient returned to 60 mg/day prednisone in at 6 months after his initial presentation, which resulted in a substantial improvement in both a- and b-wave amplitudes (DA 10.0 cd*s/m^2: b-wave – right eye – 103μv, left eye – 81μv) within 2 months. Towards the end of the first year of follow-up, good control of the patient's underlying oncologic disease was achieved, with a significant reduction in both lesion size and PET-CT signal. Overall, these results suggest a mild response to steroid treatment and a potential decrease in the need for steroids with effective management of the primary tumor.

The patient began steroid-sparing treatment with a starting dose of 50 mg/day azathioprine (Imuran®) and 40 mg/day for five days, every three weeks of intravenous immune globulin (IVIG) 15 months after presentation. Upon increasing azathioprine dosage to 150 mg/day, he developed allergic reactions, liver enzyme elevations, and profound neutropenia (Absolute neutrophil count <500). As a result, azathioprine treatment was discontinued, and only IVIG was administered until patient's blood count normalized. During this period, the patient's ERG b-wave responses fluctuated between 50 and 100μv, well below the lower normal values for his age group (235μv).[8] PET-CT performed 17 months after the initial presentation, showed an increased signal emanating from the patient's subcarinal metastasis, which had previously remained stable at around 2.7cm. It was, therefore, decided to excise it by left thoracotomy.

Starting at 20 months following presentation, there was a significant clinical improvement in the patient's subjective vision, despite a moderate decrease in b-wave responses on ERG (DA 10.0 cd*s/m^2: b-wave - right eye from 75μv to 61μv, left eye from 100μv to 72μv, from 16 months to 20 months of follow-up, respectively). This coincided with continuous steroid tapering, finally reaching 5 mg/day of prednisone after 26 months (Supplemental Fig. 3). A month later, new hypermetabolic subcutaneous processes on the patient's back and right thigh, as well as several femoral lesions, were observed on PET-CT. Following these findings, pembrolizumab (Keytruda®) 200mg IV every 3 three weeks was started at 33 months of follow-up. An ERG performed at 39 months of follow-up showed a substantial improvement in retinal function, seen in both a- and b-waves (Figs. 1A and 5), accompanied by an increase in macular thickness on OCT (Figs. 1B and 2) and a subjective clinical improvement.

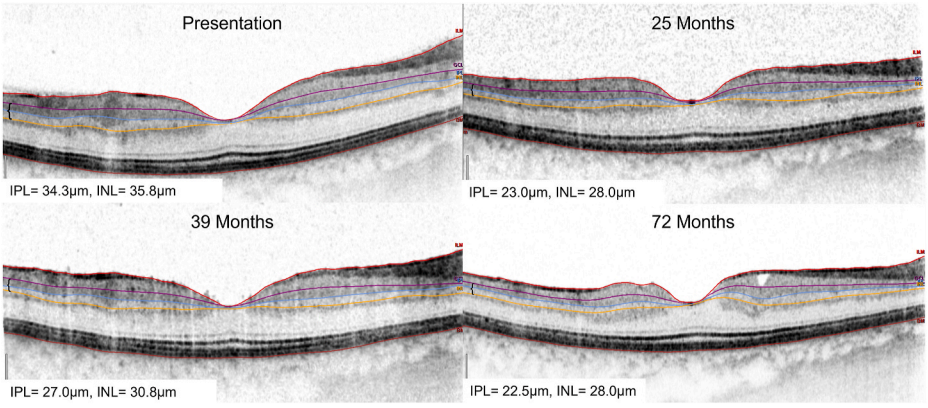

Fig. 2. Macular OCT of the right eye at four time points: initial presentation (**A**), before pembrolizumab treatment (25 months, **B**), post-pembrolizumab treatment (39 months, **C**), and at the final follow-up visit (72 months, **D**). Brackets indicate the IPL and INL layers, which showed the most significant change in thickness throughout the follow-up.

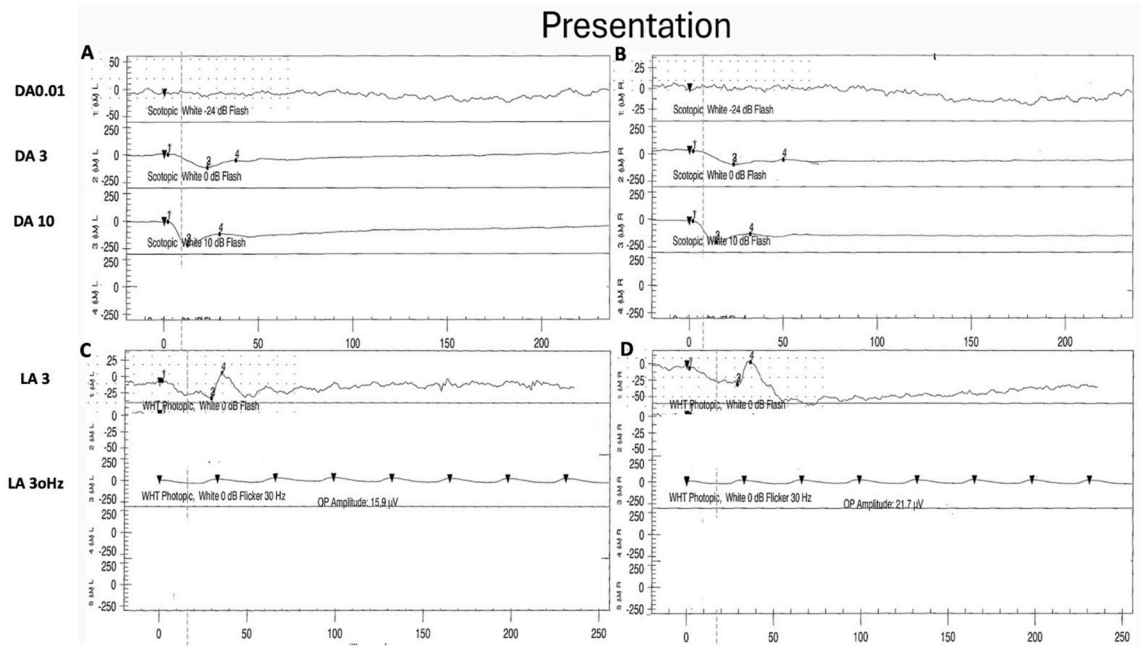

Fig. 3. Full-field electroretinography (ERG) performed at the time of presentation accordance with the ISCEV protocol. The top panels (A, B) display dark adapted responses, while the bottom panels (C, D) show light adapted and flicker responses, for the left eye (A, C) and the right eye (B, D).

Starting early in his 4th year since presentation, the patient was considered melanoma-free. Due to the Covid-19 pandemic, three of the IVIG treatments were not administered. This may correlate with a minor reduction in scotopic ERG waves in at 43 months of follow-up. However, ERG responses showed a continued improvement trend (Fig. 1A) with subsequent stabilization until the 43rd month of follow-p. A moderate reduction in ERG a- and b-waves and macular thickness on OCT was observed towards the end of the 5th year, with no apparent clinical correlation.

OCT macular imaging suggests that the early impact of MAR is more pronounced in the outer macular ring (as defined by the EDTRS grid), with milder changes in the pericentral macular ring and central fovea. Those are presented in Supplemental Fig. 1, showing similar yet less pronounced trends. Overall, as predicted by the ERG a- and b-wave measurements, the change in total retinal thickness shown by OCT throughout the patient's follow-up was explained by changes in the inner retina (Fig. 4A), mainly within the inner nuclear (INL, Fig. 4B) and inner plexiform (IPL) layers (Fig. 4C). No substantial changes were observed in the outer retina, with a maximal difference within 10 µm (Supplemental Fig. 2).

As of the middle of the patient's 7th year of follow-up, his optic nerve functions remained preserved, besides a moderately reduced peripheral VF. Similarly, the patient's subjective symptoms, OCT, and ERG findings remain stable under pembrolizumab treatment (Supplemental Fig. 5).

3. Discussion

Over the past decade, the introduction of ICI dramatically improved the prognosis of advanced melanoma patients and became standard treatment practice. As a result, the need for accurate long-term follow-up of MAR patients and a deeper understanding of the condition's natural history has become more relevant than ever. To the best of our knowledge, this case is the most extended and most detailed follow-up of a MAR patient to date, described throughout seven years of frequent fundus examination, VA, VF, OCT, and ERG testing. This study suggests that ERG is a valuable tool for detecting early retinal changes indicative of MAR, complementing the structural changes observed on OCT. This may be highly relevant in patients with a history of melanoma, as MAR may be the first sign of systemic metastatic disease. Furthermore, this study supports the early initiation of biological treatment in MAR patients as a potent disease-modifying therapy.

To date, there has only been one large case series published in 2001 by Keltner et al., which aggregated all 62 MAR patients.[3] Of the MAR cases described in the two decades that followed, only three case reports described pembrolizumab treatment,[5,9,11] one described a combined Ipilimumab/Nivolumab treatment in a three-case series,[10] one case report described Ipilimumab treatment[12] and one report described MAR possibly triggered by Nivolumab treatment.[13] Our report thoroughly describes an improvement in autoantibody-positive MAR after the use of a PD-1 inhibitor (pembrolizumab), as demonstrated by subjective resolution of the patient's visual symptoms and a substantial improvement in macular retinal thickness on OCT and retinal function on ERG.

As in our case, most reported MAR cases were preceded with a diagnosis of cutaneous melanoma. However, MAR has also been described in association with mucosal[4] and ciliochoroidal[11] melanoma or with a melanoma diagnosis only after MAR syndrome onset.[3] In the present case report, the patient was already scheduled for a routine PET-CT follow-up, which closely coincided with the onset of his visual symptoms. This highlights the need for close monitoring of the oncological status of cutaneous melanoma patients who develop new visual symptoms, with or without fundoscopic changes.

In MAR patients, routine ophthalmological examinations may often be normal or show only minimal fundus changes throughout follow-up. Furthermore, patients typically tend to retain near-normal visual acuity, color vision, and central visual field, although these may deteriorate as the disease progresses.[3] As a result, sensitive, objective tests are necessary so as not to delay MAR diagnosis. OCT is a particularly useful tool in the evaluation of macular diseases and may be used to detect the retinal structural changes associated with advanced MAR. However, as in previous cases, OCT imaging of our patient's macula was normal on presentation, only showing substantial thinning approximately six months after the initial symptom onset[5,9,10] (Fig. 1). ERG, on the other hand, is a test that measures the electrical activity of the retina in response to light stimulation. In our case, an ERG performed at presentation already showed the hallmark reduction in b-wave amplitude indicative of bipolar cell dysfunction, with a preserved a-wave response. This may

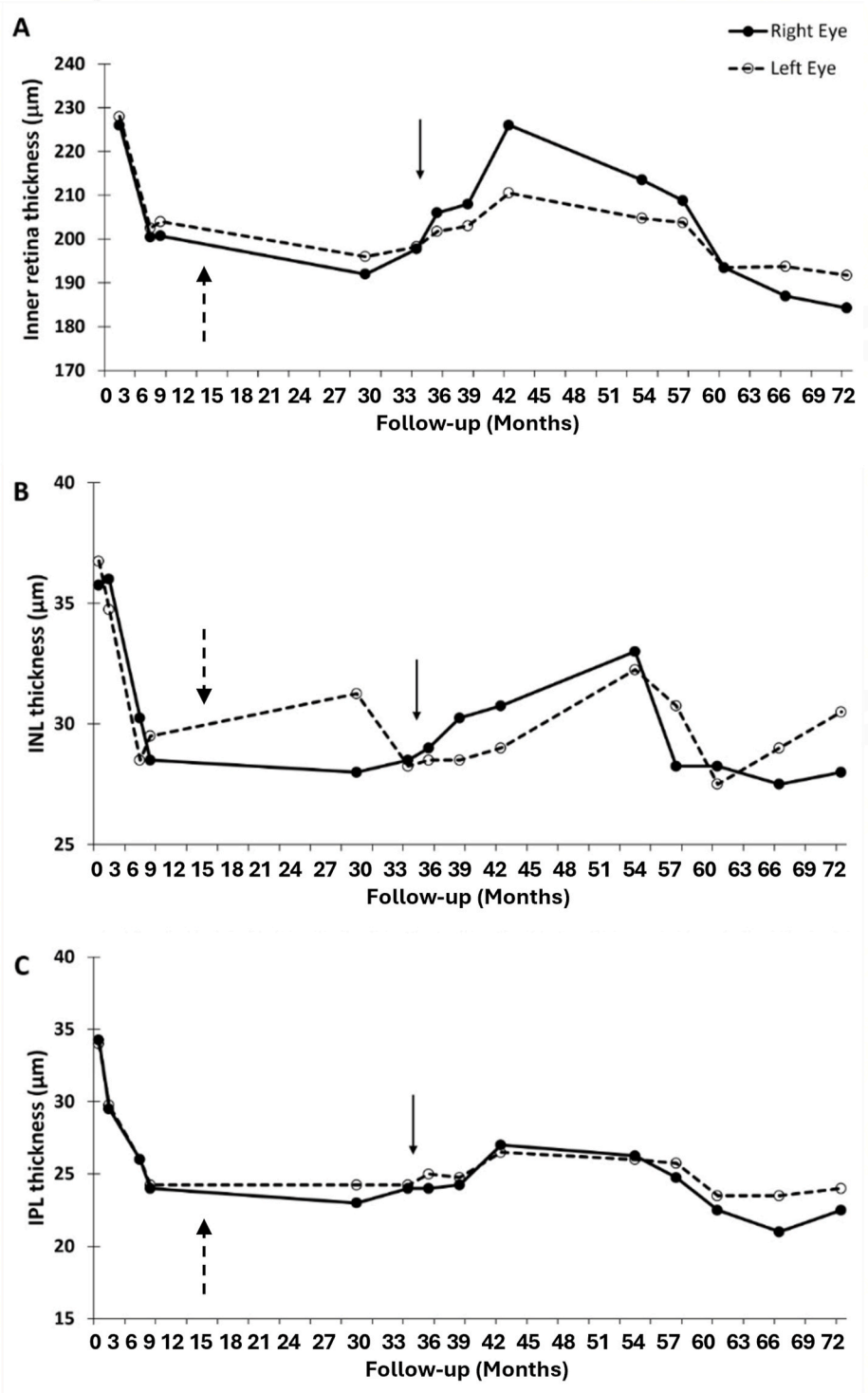

Fig. 4. **A-** OCT thickness of inner macular layers (from the external to the internal limiting membranes) at the outer macular ring (defined by the EDTRS grid) over seven years in the right (closed circles) and left (open circles) eye indicates an initial thinning of inner layers at the outer macular ring, followed by improvement following initiation of pembrolizumab treatment (arrow). **B and C-** OCT thickness of the inner nuclear layer (INL, panel B) and inner plexiform layer (IPL, panel C), at the outer macular ring, representing the bipolar cells and their axons, respectively, and accounting for a substantial part of the change in retinal thickness. Right eye – closed circles. Left eye – open circles. The dashed line arrow indicates the initiation of azathioprine and IVIG and the solid black arrow indicates the initiation of pembrolizumab treatment.

further highlight the importance and sensitivity of ERG in the early diagnosis of MAR, given its specificity for bipolar cell function, in contrast to the late structural changes detected by OCT. Notably, structural changes on OCT lagged by approximately six months compared to changes on ERG, yet similar trends were observed between these modalities during the follow-up period. These findings suggest that OCT may serve as a valuable tool for subacute MAR patient follow-up and assessment of treatment efficacy.

Further analysis of OCT data showed that the major changes in retinal thickness were localized to the outer macular ring of the inner

nuclear (INL) and inner plexiform (IPL) layers, which contain the bipolar cells and their axons, consistent with the pathophysiology of MAR. As recovery from neuronal loss is not possible, OCT retinal thickening in our case may be attributed to correction of synaptic abnormalities, or to subclinical cystoid or glial changes. These findings highlight the potential value of specific layer segmentation in refining the differential diagnosis, as compared to the commonly used parameter in the clinical setting, total macular retinal thickness (Fig. 4).

Due to its extremely low prevalence, there is a marked absence of controlled trials regarding the treatment of MAR. However, two major synergistic approaches have been suggested for managing the symptoms and complications of MAR.[5] Immunosuppressive therapy is used to address MAR's antibody-mediated pathophysiology. Indeed, in the case of our patient, treatment using glucocorticosteroids, azathioprine, and IVIG during the patient's first three years of follow-up resulted in symptomatic and electrographic improvement (Fig. 1). Additionally, cytoreductive management of the underlying metastatic malignancy may act to reduce the burden of antigenic stimulation and allow antibody clearance.[5] In our case, the patient had an excellent oncologic response to pembrolizumab treatment, which correlated with b-wave elevation and a significant improvement in visual symptoms. While it has been previously suggested that concurrent high-dose corticosteroid and anti-PD-1 therapy may be associated with poorer outcomes,[14] it should be noted that in our case, the patient did not receive a dosage over 10mg/day of prednisone since starting pembrolizumab treatment. Furthermore, a concern has previously been raised that immune upregulation may trigger or exacerbate MAR through further T-cell activation.[10,11] Cohen et al.[13] recently reported a unique case of unilateral MAR associated with TRMP1 antibodies, possibly triggered by immunotherapy with Nivolumab used to consolidate melanoma remission. In their case, it was discontinuation of the ICI which led to both symptomatic improvement and recovery of inner-retinal function on ERG. This outcome stands in contrast to our findings, underscoring the complex interplay between immune modulation and control of the baseline disease driving antigenic stimulation.

In conclusion, the evolution of treatments for metastatic melanoma has brought an increase in patient survival, creating the need for accurate tools for continuous, long-term follow-up. In this case, we underscore the potency of ERG as a tool for early diagnosis of MAR and observe a structure/function correlation by assessing OCT inner macular layers and ERG b-wave amplitude. These findings underscore the value of a multi-modal approach to patient follow-up. Furthermore, we report substantial improvement in retinal function following pembrolizumab treatment in an antibody-positive MAR patient, who was previously treated with corticosteroids, azathioprine and IVIG. Though our study is limited to the follow-up of a single patient, it highlights the potential benefits of early immunotherapy, particularly in antibody-positive MAR patients. Further studies with standardized intervals of ERG and OCT testing in a larger cohort of MAR patients are warranted.

CRediT authorship contribution statement

Raz Tshuva-Bitton: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Michael Ostrovsky:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. **Vicktoria Vishnevskia-Dai:** Writing – review & editing, Supervision, Investigation. **Nancy Agmon-Levin:** Writing – review & editing, Supervision, Investigation. **Ifat Sher:** Writing – review & editing, Visualization, Methodology. **Ygal Rotenstreich:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Patient consent

A written informed consent for the publication of the patient's clinical details was obtained.

Authorship

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

Funding

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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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2025.102307.

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