Case Reports in Ophthalmology

Case Rep Ophthalmol 2023;14:498–506
DOI: 10.1159/000533769
Received: May 22, 2023
Accepted: August 17, 2023
Published online: October 6, 2023

Case Report

Unilateral Melanoma-Associated Retinopathy Case Report

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Keywords

Electronegative electroretinogram · Melanoma-associated retinopathy · Paraneoplastic syndrome · Autoimmune retinopathy · Antiretinal antibodies

Abstract

In this report, we present a case of unilateral melanoma-associated retinopathy in a 72-year-old woman. The patient's main symptoms were decreased vision and positive dysphotopsia. Unilateral electronegative electroretinogram (ERG) was suggestive for melanoma retinopathy. PET-CT discovered metastatic disease, 3 years after the initial melanoma. A prompt treatment with corticosteroids was started, followed by immunotherapy. The central and peripheral vision of the patient improved, and the ERG showed normalization of the responses. This case highlights the importance of early recognition and individualized treatment strategies for melanoma-associated retinopathy.

Introduction

Melanoma-associated retinopathy (MAR) is a rare acquired autoimmune retinal disease occurring in patients with melanoma. It typically presents years after the diagnosis of malignant melanoma, but in some cases MAR can be present before the tumor has been diagnosed. In cases of metastatic melanoma, the latency period is usually shorter and can be less than a year. A personal or familial history of autoimmune disease is defined as a risk factor for MAR [1].

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The pathologic processes remain poorly understood. It is hypothesized that epitopes of the melanoma cells are presented to the immune system. These epitopes are similar to ones found on retinal cells and trigger a cross-autoimmune response [2]. The immune response that occurs in patients with MAR is located at the level of the retinal ON bipolar cells, disrupting neural transmission with associated rod photoreceptors. To date, several proteins have been found being able to generate such a response. These include the 35-kDa Müller protein, a 22-kDa neuronal antigen, and a membrane-associated 33-kDa protein. In addition, certain ion channels including the transient receptor potential cation channel subfamily M member 1 (TRPM1), specifically expressed in retinal ON bipolar cells, can serve as an antigen [3]. Since there are multiple potential targets, the generated immune response can have several origins with diverse clinical manifestations [4].

Symptoms associated with this form of retinopathy include positive visual phenomena, such as photopsia, and a decrease in visual acuity or visual field defects. Night vision may also be affected since the rod photoreceptor signaling is disturbed. The symptoms commonly manifest bilaterally. Since the symptoms are nonspecific, the condition is often misdiagnosed or missed [5].

Subtle retinal changes can be found in the early stages of MAR. The electroretinogram (ERG) helps in establishing the diagnosis. Typically, it shows a normal photopic response and a reduced scotopic response. The response is characterized by preserved a-wave and reduced b-wave, known as an electronegative ERG [6]. The presence of serum autoantibodies against retinal bipolar cells further confirms the diagnosis. Based on previous studies, antibodies are present in up to 40–65% of patients with autoimmune retinopathy. Although MAR is a diagnosis of exclusion, it is important to establish diagnosis at an early stage as this lowers the risk of irreversible damage to the retina [5–7].

There is no established consensus concerning the treatment of MAR. Current treatment protocols are based on case reports and generally consist of cytoreduction of the underlying melanoma and immunotherapy. By cytoreductive treatment, tumor cells regress, reducing the stimulus for antigen production. Immunotherapy aims to reduce levels of circulating autoantibodies [5, 8]. Short courses of high-dose intravenous prednisone or oral treatment have been used by themselves or in combination with plasmapheresis [9]. Other studies have shown a good response obtained by administration of biologics and intravenous immunoglobulin [8].

Case Presentation

A seventy-two-year-old female presented with progressive vision loss since 2 weeks, predominantly in the right eye. In addition, she experienced positive visual phenomena such as persistent shimmering lights. Hemeralopia was not present. The patient reported that she has never experienced any direct exposure of laser or light to her eyes.

Best-corrected visual acuity was Snellen 0.5 and 0.9 in the right eye and left eye, respectively. Slit-lamp examination was normal, and intraocular pressure and ocular motility examinations were unremarkable. Fundoscopic examination showed discrete vascular attenuation with subtle pigment epithelium alterations (Fig. 1). Neuro-ophthalmologic examination revealed red desaturation on the right eye with minimally reactive pupils, without relative afferent pupil defect.

Her general medical history was noted for cutaneous malignant melanoma in the pretibial region of her right leg, diagnosed 3 years ago. The malignant melanoma had a Breslow thickness of 0.82 mm and was treated by surgical wide excision. Pathological examination showed invasion through the papillary dermis, which led to a Clark 3 staging. The sentinel

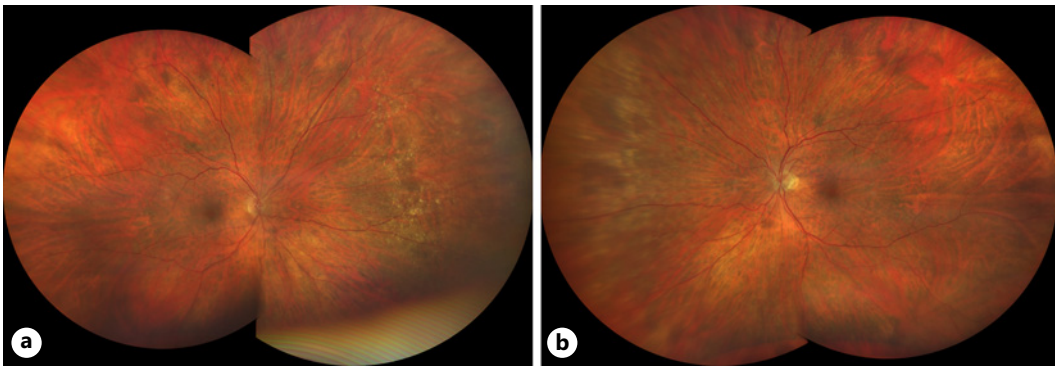

Fig. 1. Fundus photography showing vascular attenuation and retinal pigment mottling. **a** Right eye. **b** Left eye.

node was clear of tumor cells. Pathological staging was pT1bN0M0, stage IA, according to the 8th AJCC staging. Further relevant medical history included arterial hypertension and atrial fibrillation. Current medication consisted of beta blockers, statins, and vitamin supplementation.

Investigations

OCT scan examination revealed foveal disruption of ellipsoid and interdigitation zone with normal foveal depression in both eyes (Fig. 2). Fluorescein angiography showed no signs of retinal vasculitis or other vascular pathology, although minor leakage of dye from the optic disc was noted in the late phase (Fig. 3). Automated perimetry examination with an Octopus Field Analyzer showed generalized suppression in the right eye (Fig. 4). The left eye's examination was also aberrant but showed a remaining paracentral island.

Considering her medical history of melanoma in combination with the currently presenting visual phenomena and abnormal visual field examination, further investigation was done using full-field flash ERG (Fig. 5). This showed marked asymmetry of the responses between both eyes, with the right eye being severely affected. The dark adapted 0.01 Cd/m-1 showed extinguished responses. The maximal combined 3.0 and 10.0 Cd/s ERG in the right eye showed electronegative morphology with severely reduced b-wave, while the a-wave was only mildly affected. Oscillatory potentials were reduced. The photopic ERG showed an abnormal broad a-wave and mildly reduced b-wave in the right eye under light-adapted conditions with delayed latencies. In the left eye, a normal a- and b-wave were noted. Combining the history of melanoma with the asymmetric electronegative ERG, a putative diagnosis of MAR was made.

Brain computed tomography (CT) scan was normal. Blood samples including CRP, erythrocyte sedimentation rate, and complete blood count were within reference value. Indirect immunofluorescence analysis on retinal slices (Euroimmun) was performed, wherein patient serum was exposed to retinal antigens, and the obtained results exhibited a positive screening result for antiretinal antibodies. In addition, we performed screening for a set of neurospecific antibodies available in our institution: Hu, Yo, Ri, amphiphysin, CV2, Ma2, GAD65, Sox, Tr, ZIC4, and recoverin. The results were negative for all tested antibodies, including photoreceptor-specific antibody recoverin. Specific testing for autoantibodies against transient receptor potential melanopsin 1 (TRPM1) was not available.

The patient was promptly started on oral corticosteroids and vitamin D supplementation. Peroral methylprednisolone was started at a dose of 64 mg daily and tapered off weekly over a period of 3 months. We subsequently organized a full-body CT and positron emission

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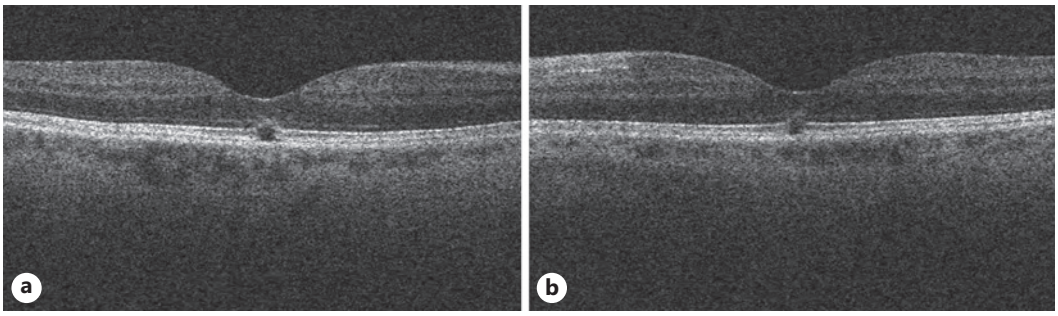

Fig. 2. OCT scan showing foveal disruption of ellipsoid and interdigitation zone. **a** Right eye. **b** Left eye.

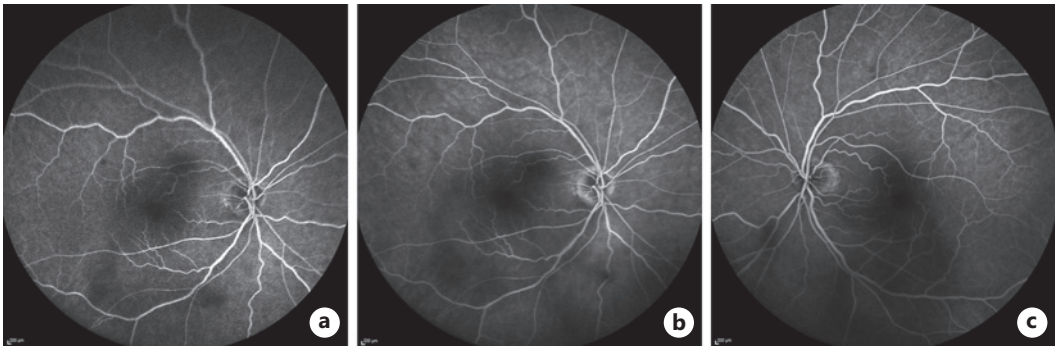

Fig. 3. Fluorescein angiography. **a** Early arteriovenous phase (right eye). **b** Late venous phase (right eye). **c** Late venous phase (left eye).

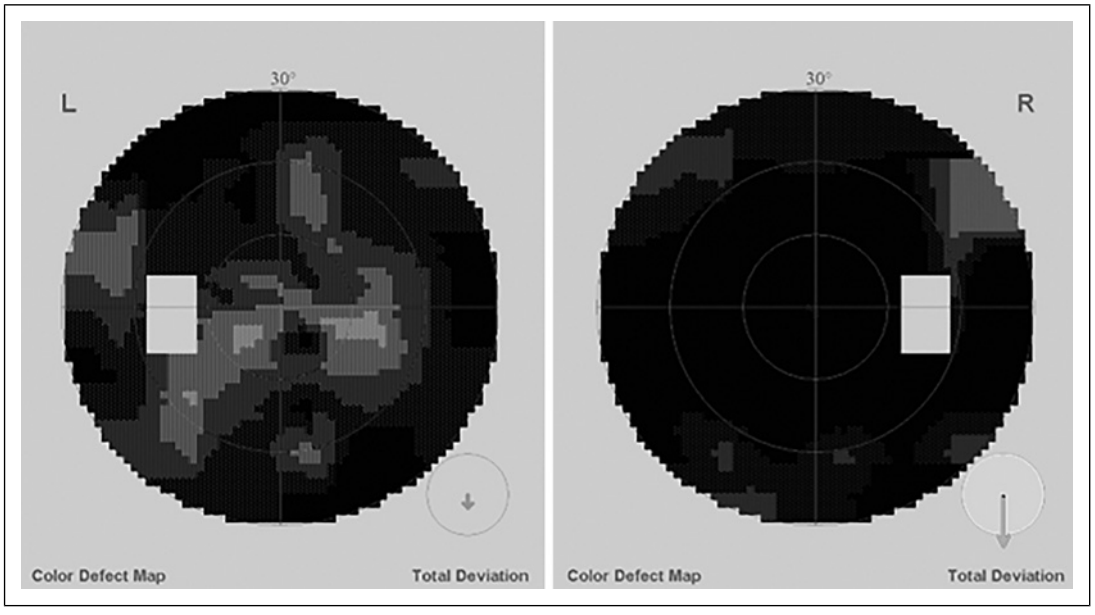

Fig. 4. Octopus perimetry showing general visual field depression in both eyes.

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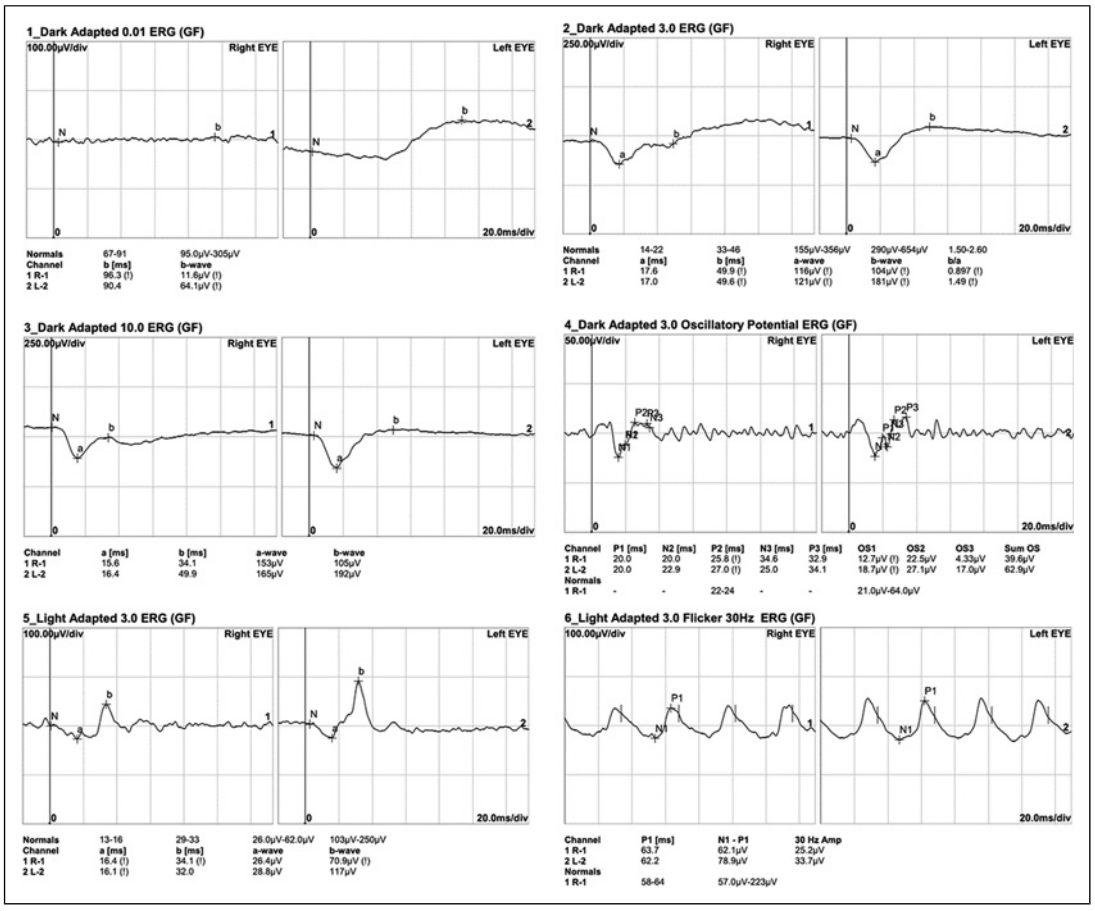

Fig. 5. Full-field ERG showing an electronegative ERG reflecting inner retinal dysfunction in the right eye.

tomography scan, which showed uptake of fluorodeoxyglucose at the right-sided iliac lymph node chain (Fig. 6). Suspecting local recurrence, an excisional biopsy of the lymph nodes was performed. Pathological investigation revealed tumor proliferation with melanocytic differentiation. The patients' retinopathy ultimately revealed a systemic manifestation of her previous local dermatological problem. Consequently, the melanoma was staged as a pT1N1M0 disease, prompting the initiation of immunotherapy with pembrolizumab.

Six weeks after the initiation of corticosteroid therapy, the patient reported an improvement of vision and disappearance of the positive visual phenomena. Objectively, vision remained, but a marked improvement of the visual field examination was noted, with only a remaining arc scotoma in the superior sector (Fig. 7). Posttreatment ERG showed improvement in both eyes with normalization of the b-wave in the right eye (Fig. 8).

Discussion

MAR is a rare condition. We report a case with asymmetric retinal involvement, both in symptoms and in ERG changes. Symptoms were more pronounced in the right eye, and the ERG showed primarily electronegativity in this eye. To our knowledge, only a few unilateral MAR cases have been described in the literature [10]. The asymmetry is possibly a sign of early disease stage. In the presented case, treatment with corticosteroids resulted in

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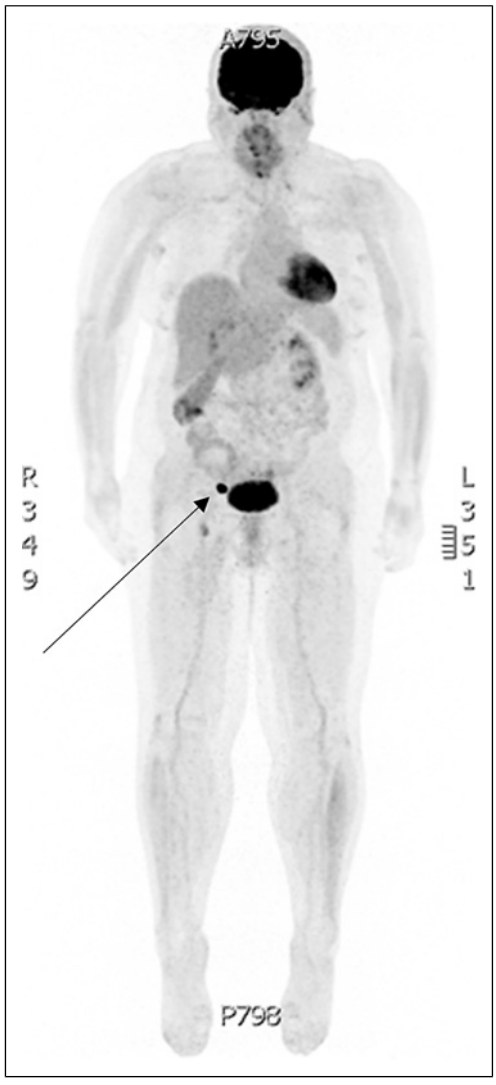

Fig. 6. PET-CT scan showing uptake of FDG glucose of the regional distant lymph node at the right-sided iliac lymph node chain, indicated by the arrow.

improved vision and normalization of the ERG, showing that if the condition is diagnosed in a timely fashion, this can improve the visual outcome. As pembrolizumab had not been administered before the first follow-up appointment, the observed effects could be predominantly attributed to the corticosteroid treatment.

The OCT examination revealed foveal disruption of the ellipsoid layer and interdigitation zone, indicating potential damage to the photoreceptor. However, no improvement was observed in subsequent follow-up appointments. While coexisting retinal diseases, such as previous solar or laser maculopathy, could potentially account for these findings, no supporting evidence or arguments were found in this case to substantiate this possibility.

The presence of antiretinal bodies was confirmed through positive immunohistochemistry testing. However, no specific antibody could be detected by the available tests. Therefore, definitive conclusions could not be drawn based on the serology. ERG is sensitive and the diagnostic tool of choice; it should be performed in any patient suspected of MAR, even in unilateral cases. A PET-CT scan is advised to detect metastatic disease if this has not already been done. The diagnosis of MAR is difficult and therefore often delayed. With this case report, we hope to improve awareness of MAR and stress the importance of early

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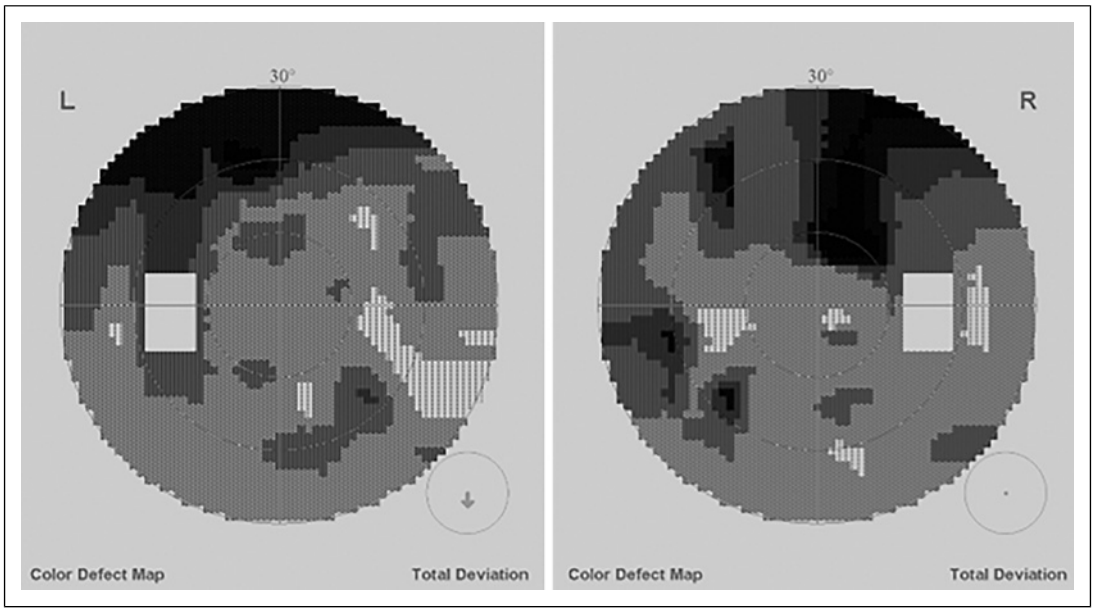

Fig. 7. Octopus perimetry showing improvement of the visual field defects of both eyes with persisting arcuate scotoma in the upper sector.

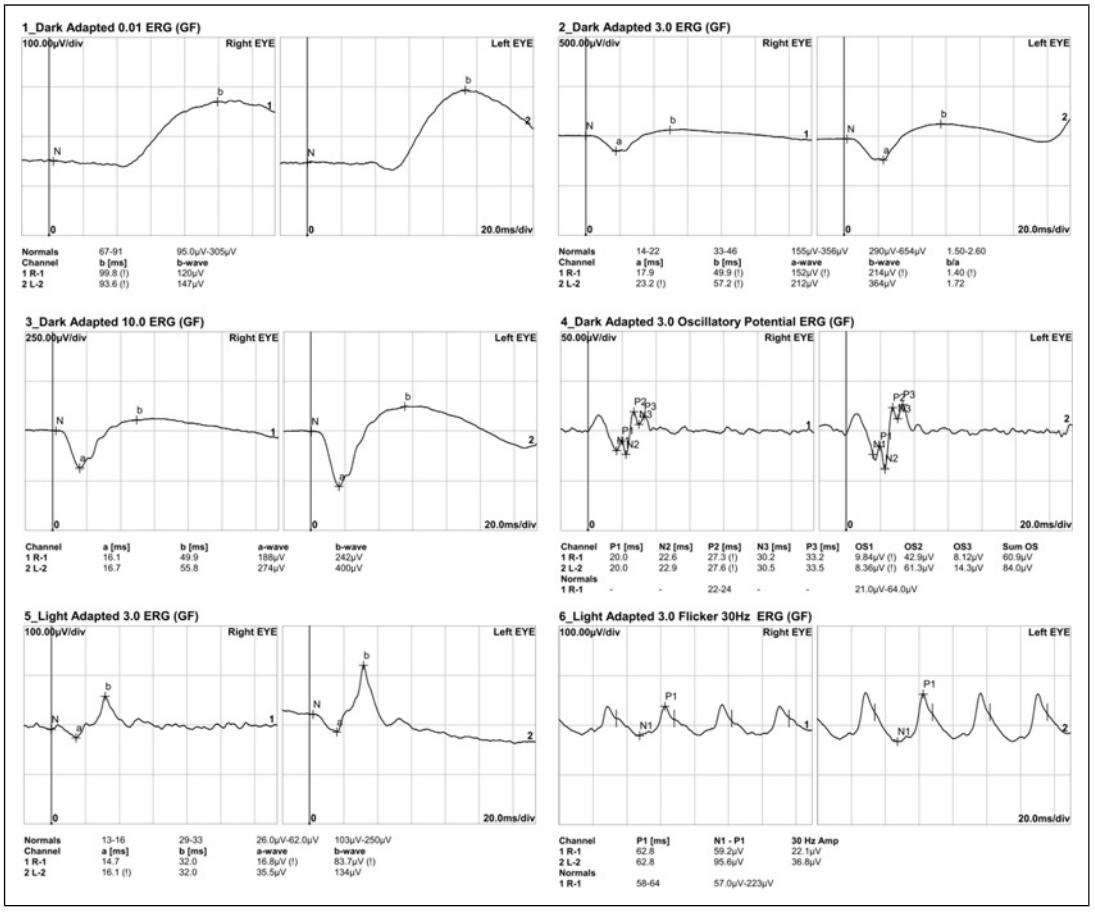

Fig. 8. Full-field ERG after peroral glucocorticoid treatment showing recuperation of b-wave in the right eye.

diagnosis to increase therapy success for both MAR and the underlying melanoma. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533769).

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study protocol was reviewed and approved by "Ethische commissie onderzoek UZ/KU Leuven (EC onderzoek)", with approval number S67668.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received relevant to this case report.

Author Contributions

Reinout Peeters: writing – original draft, review and editing; Julie Jacob: writing – review and editing and resources; Freya Peeters and Ingele Casteels: writing – review and editing; Dafina Draganova and Koen Poesen: writing – review and editing and laboratory evaluation; and Irina Balikova: conceptualization, writing – review and editing, and supervision.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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