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CLINICAL CASE REPORT

Melanoma-associated retinopathy during pembrolizumab treatment probably controlled by intravitreal injections of dexamethasone

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Abstract
Purpose Melanoma-associated retinopathy (MAR) is a rare paraneoplastic syndrome due to antibodies targeting bipolar retinal cells. Its evolution, particularly in patients treated with immune checkpoint inhibitors (ICI), is currently poorly understood. In the few cases published, patients' visual function got worse when these molecules were prescribed. Here, we present a case of a patient with severe MAR treated with an ICI for melanoma progression.
Methods A 68-year-old woman with a history of melanoma of the palpebral conjunctiva presented with sudden and gradually worsening visual disturbances. Simultaneously, a metastatic evolution of the melanoma was diagnosed and surgically treated exclusively. Visual acuity assessment, static automated perimetry and ERG results lead to the diagnosis of MAR. Since systemic corticosteroid therapy did not improve her symptoms, repeated intraocular corticosteroid injections were performed with a positive outcome. Later on, metastatic progression of the patient's melanoma led to the introduction of pembrolizumab, an ICI targeting PD-1. Immunotherapy has changed the prognosis of patient affected by metastatic melanoma, but these molecules may induce various immune-related adverse effects. In our case, intraocular corticosteroid injections were still performed simultaneously. Visual acuity assessment, static automated perimetry and ERG were performed during the course of this treatment.
Results Full-field ERGs results suggested the possibility that the ophthalmologic treatment might restore the patient's retinal function despite the continued immunotherapy.
Conclusion We report the first case of MAR with a positive outcome after 1 year of ICI, possibly thanks to intravitreal corticosteroid therapy.

Keywords Autoimmunity · Paraneoplastic syndromes · Paraneoplastic syndromes, Ocular · Melanoma-associated retinopathy · Immune checkpoint inhibitor · Pembrolizumab

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Introduction

Melanoma-associated retinopathy (MAR) is a rare paraneoplastic complication of melanoma, occurring mostly in metastatic stages. Antibodies directed against melanoma antigens cross react with the retinal

bipolar cells which transmit the message from photoreceptors to ganglion cells [1–4]. Typically, symptoms include: flickering or shimmering photopsias, constriction of the visual field, and some degree of night blindness. With recent therapeutic advances in metastatic melanoma and the increase in patients' overall survival, this rare syndrome has been more frequently reported. ERG is fundamental for the diagnosis and reflects specifically altered ON-bipolar cell function with a functional preservation of photoreceptors [5, 6].

PD-1 inhibitor monoclonal antibodies are indicated in the treatment of advanced or metastatic melanoma and as adjuvant treatment of stage III and stage IV [7]. They enhance the immune system response against cancer cells. Hence, their main side effects are mostly immune-related adverse effects.

Here, we document the case of a patient with severe MAR treated by intravitreal injections of dexamethasone and who has been receiving pembrolizumab to treat her metastatic melanoma for more than a year. To our knowledge, this is the first case of MAR without an unfavorable evolution under anti-PD-1 therapy. We presume that this was allowed by the concomitant use of intravitreal corticosteroid therapy.

Case report

A 68-year-old Caucasian woman, whose past medical history included only high blood pressure and amblyopia of the right eye since childhood, without personal or family history of autoimmune or neoplastic diseases, was referred for an ulcerated achromic melanoma of the right upper palpebral conjunctiva with a Breslow thickness of 5 mm (stage IIc). B-RAF mutation was not detected. Appropriate excision was performed, followed by several palpebral reconstructions.

Two years later, the patient was diagnosed with typical bilateral granulomatous anterior uveitis and was successfully treated with corticoid eye drops.

A few months later, she had a decrease in visual acuity, related to inflammatory episode of the posterior segments in both eyes with hyalitis. Etiology of these manifestations was not found, but the patient was successfully treated with oral corticosteroid therapy. At the same time, a CT-scan detected an isolated nodule on the right adrenal gland. Pathological analysis of the complete excision revealed a melanoma metastasis with no B-RAF mutation detected. At the time, no adjuvant treatment was recommended.

Three years after the initial diagnosis, the patient developed a vitiligo. Concomitantly, she complained again of a sudden and gradually worsening visual disturbance characterized by hazy vision, small moving gray circles, and important photosensitivity, while night vision remained subjectively normal. PET-scan revealed no new melanoma metastasis. Ophthalmic evaluation objectified a significant visual loss with a visual acuity in decimals of 1.6/10 in the right eye (RE), 2/10 in the left eye (LE) instead of 5/10 RE and 10/10 LE previously. Slit-lamp biomicroscopy showed bilateral early nuclear cataract, probably promoted by uveitis and corticosteroids. However, bilateral phacoemulsification did not improve her symptoms and visual acuity continued to fall down to $<$ 1/20 RE and 2/10 LE. Static automated perimetry testing was deeply altered in a diffuse way, especially in the periphery (Fig. 1a). Intraocular pressure, color vision, fundus autofluorescence imaging (30°- and 55°-field, Combined Heidelberg Retina Angiograph), and spectral domain optical coherence tomography were normal (Spectralis OCT device (Heidelberg Engineering, Dossenheim, Germany). A full-field electroretinography (Ff-ERG) was performed according to the guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV) [8] using a Ganzfeld apparatus (Ophthalmologic Monitor, Métrovision, Pérenchies, France). The dark-adapted (DA) 0.01 ERG was undetectable (Fig. 1b). The DA 3.0 ERG has a mild reduced a- and b-waves with a ratio *b*/*a* of 0.3 instead of 2.5 for the age-matched control. In light-adapted (LA) single flash (SF) ERG, the a-wave is normal, but the b-wave is reduced in comparison with the age-matched control. The implicit times for DA 3.0 ERG, DA 3.0 and LA 30 Hz FL were longer in the patient in comparison with the age-matched ERG values (44 ms versus 33 ms for DA 0.01). This negative-ERG pattern with a b/a ratio below 1 indicating a selective dysfunction of ON- bipolar cells is herein in line with the diagnosis of melanoma-associated retinopathy. Such a negative-ERG is also encountered in several inherited retinal disorders, i.e., congenital stationary night blindness, X-linked retinoschisis, and retinal dystrophy of neuronal ceroid lipofuscinosis 3 (CLN3). The presence of anti-TRPM1 antibodies in the patient's serum was

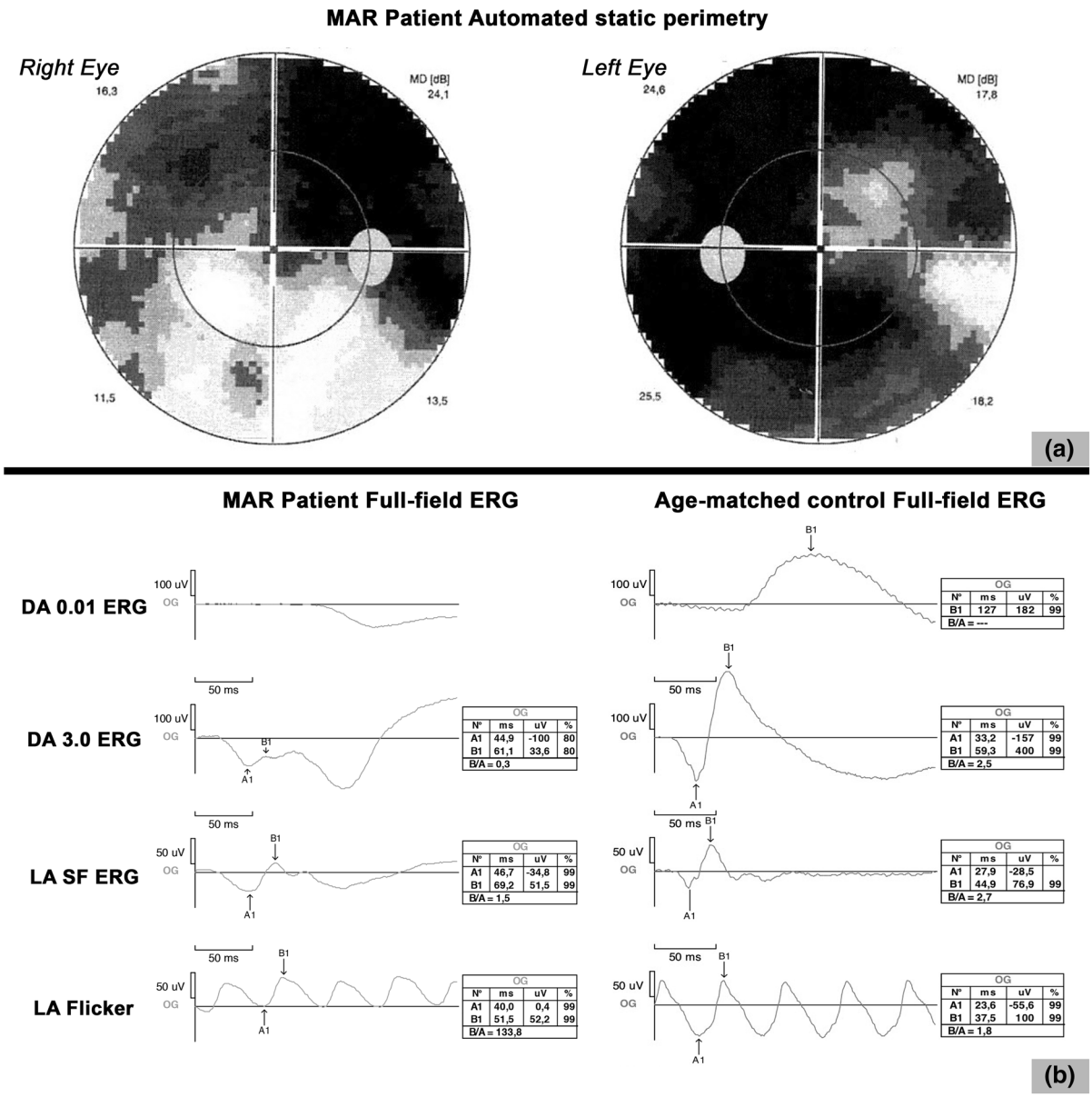

Fig. 1 Initial data from our patient's ophthalmological examinations (**a**) retinal sensitivity impairment with central and pericentral scotoma more pronounced in the left eye on automated static perimetry (**b**) full-field ERG of the patient and an age-matched control, only one eye. The rod specific response (DA 0.01) is undetectable. The dark-adapted (DA) 3.0 ERG has a normal a-wave (-100 µV for the patient versus − 157 µV for the control) and severely attenuated b-wave (33.6 µV for the patient versus 400 µV for the control). The photopic single flash light-adapted (LA SF) ERG has a normal a-wave amplitude (− 34.8 µV versus − 28.5 µV for the control) and a moderate reduced b-wave amplitude (− 51.5 µV versus − 76.9 µV for the control). The 30-Hz flicker is reduced in amplitude with a mildly abnormal implicit time in comparison with the control response

confirmed by different methods previously reported by Varin et al. [9]: the patient's serum labeled two isoforms of TRMP1 during immunolocalization studies on cells overexpressing the different isoforms of human TRMP1, it detected three isoforms in western blot analysis, and reacted with TRMP1 on mouse retinal cryosections. Despite the presence of vitiligo and uveitis, the patient's symptoms and the context

were not suggestive of a Vogt–Koyanagi–Harada syndrome.

After oral corticosteroid therapy failed to improve her symptoms, intravitreal dexamethasone injections (700 µg/injection) were performed every 6 months, allowing an improvement in visual acuity, measured at 2/10 RE and 4/10 LE after 2 months.

Unfortunately, PET-scan subsequently revealed gastric and gallbladder metastases. Pembrolizumab 2 mg/kg/3 weeks was introduced with closer ophthalmologic monitoring, resulting in a global stability of the metastatic melanoma with subsequent PET-scan showing regression of the gallbladder metastasis and stability of the other targets. The previously diagnosed vitiligo spread considerably.

While local injections of dexamethasone were maintained biannually with good tolerance, the patient reported that ocular symptoms tended to relapse just before each injection and to improve after them with an increase in visual acuity and retinal sensibility (Fig. 2). Her visual abilities are good enough so that she can maintain her autonomy in her daily life activities. Floaters disappeared, but she still experiences photosensitivity. The full-field ERGs were performed again after iterative corticoid injections. We found that the b/a amplitude ratio of DA 3.0 ERG improved from 0.3 to 0.8, and the b-wave amplitude of 3.0 ERG increased from 33.6 to 136 µV, although the DA 0.01 ERG still remained undetectable. These results suggested the possibility that our treatments might restore the retinal function of our MAR patient.

Discussion

MAR belongs to autoimmune retinopathies (AIRs) and to the paraneoplastic subgroup, along with the better-known carcinoma-associated retinopathy (CAR), which is mainly associated with small cell lung cancer. About sixty cases were reviewed in 2011 [2], a few others were subsequently reported. In most cases, MAR occurs in the context of cutaneous melanoma, but it has been described in any type of melanoma and also in other cancers. As our case shows, discovery of melanoma usually precedes the diagnosis of MAR and the retinopathy announces or follows a metastatic evolution. It is hence compulsory to perform a re-staging assessment when MAR is diagnosed.

Pathogenic mechanism of this disease is a rod bipolar cell dysfunction due to antibodies targeting common epitopes shared between melanoma and rod bipolar cells. Like other spontaneous autoimmune clinical or biological manifestations, MAR is sometimes considered to be a good prognostic factor.

Its symptoms can be multiple and difficult to characterize, including photopsias, which are sometimes confused with a visual aura. Consequently, ophthalmologic examination must be considered for any unexplained visual disorders in a patient suffering from a melanoma.

Routine ophthalmological examination may not be discriminant, enhancing the necessity of performing early ERG not to delay the diagnosis. Visual acuity is mostly preserved or mildly reduced. Fundus examination can be normal or show retinal vessel attenuation (30%), optic disk pallor (23%), or vitreous cells (30%) [2]. Visual field assessment is typically altered with central or paracentral scotoma and peripheral constriction. Hyalitis, observed in some MAR cases, reflects the inflammation secondary to retinal aggression [2, 10]. It seems likely that the inflammatory cellular reaction may also concern the anterior chamber. However, no case of previous anterior uveitis similar to our patient's case has been reported and it is not known whether anterior uveitis can be related to MAR.

Interpretation of anti-retinal autoantibodies remains very delicate. Regularly, non-specific antibodies reactions involving various retinal components have been reported, similarly to what can be seen in other AIRs. Some of these reactions are just a consequence of retinal damages.

Nonetheless, recent studies revealed the TRPM1 cation channel to be one of the autoantigens targeted by these autoantibodies [4]. In the retina, this channel is specifically expressed by ON-bipolar cells. Moreover, TRPM1 also regulates the proliferation and differentiation of melanocytes. This gene can be down-regulated in vitiligo skin [11]. This element suggests that MAR and vitiligo, which both occurred simultaneously in our case, could share a common physiopathology.

MAR treatment remains controversial, mostly due to the limited knowledge about this disease natural evolution and to the absence of controlled trials. Treatment of the underlying neoplasm may reduce the tumor antigenic stimulation. Ophthalmological

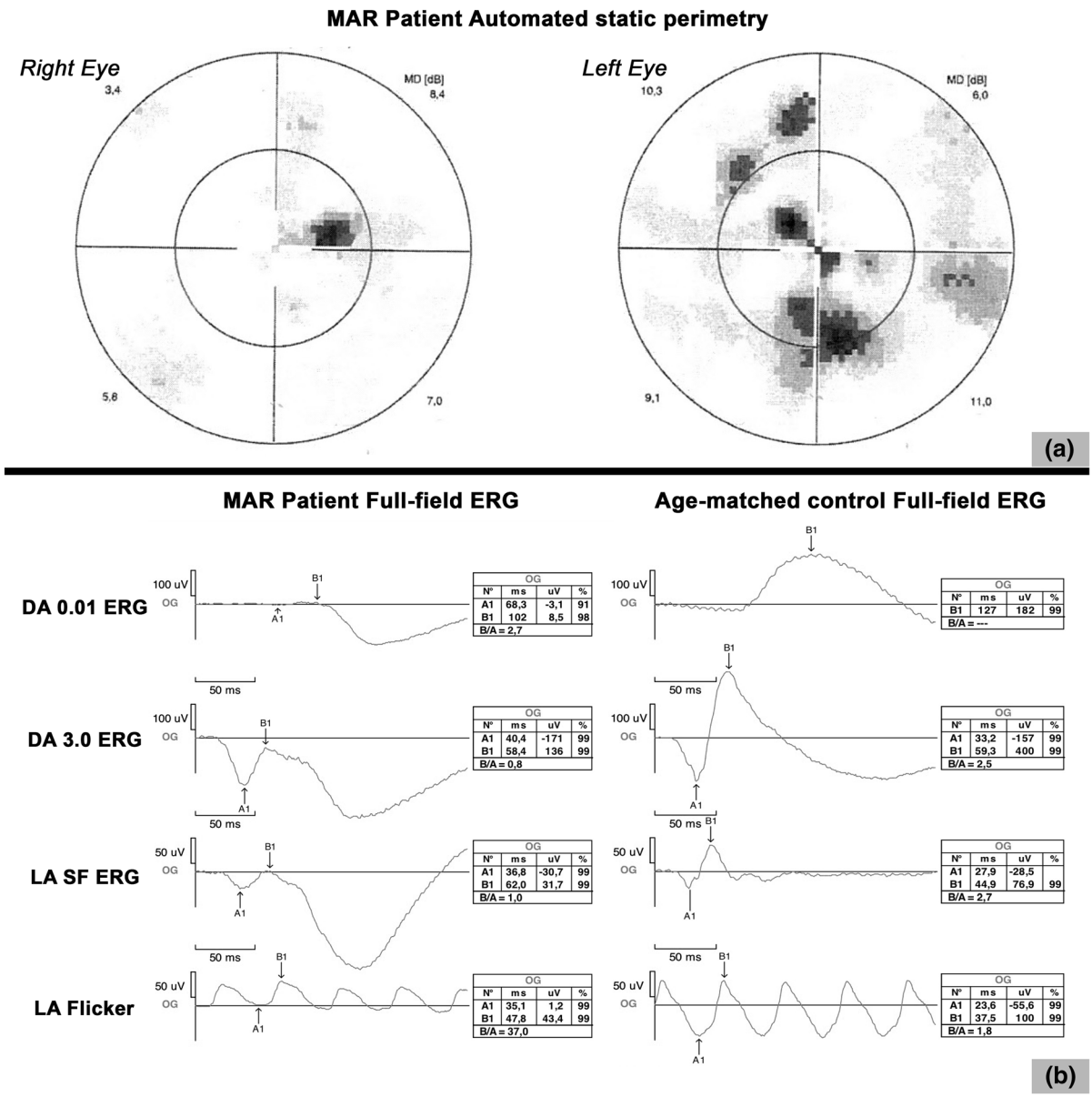

Fig. 2 Automated static perimetry and full-field ERG performed after the second intravitreal injection of dexamethasone associated with pembrolizumab (**a**) note the major improvement of the retinal sensitivity map on post treatment automated static perimetry in comparison with initial data. (**b**) Full-field ERG, only one eye: DA 3.0 ERG has still a negative-ERG pattern with a b/a ratio of 0.8 versus 0.3 for initial ERG, thus reflecting an increase in b-wave

management, including immunomodulation with intravenous immunoglobulin, plasma exchange, or oral corticosteroid therapy to reduce the retina aggression, is often disappointing [12]. However, intravitreal dexamethasone injections associated with specific melanoma treatment was efficient and acceptable in our case.

Recently, a case of MAR treated by intravitreal slow-release corticosteroid implants has been described. The patient experienced a very rapid improvement in his symptoms correlated to improvement in ERG and perimetry findings. These results were persistent after 3 years of follow-up [13]. This observation further encourages to consider intravitreal

corticosteroids as a preferred alternative to systemic corticosteroids therapy. Moreover, this treatment has less interaction with immune checkpoint inhibitor (ICI).

Only two cases of MAR during treatment with ICI have been published. The first one described a case of metastatic choroidal melanoma treated by ipilimumab (anti-CTLA-4) with initial stabilization of the cancer, but with visual acuity impairment and an increase in vitiligo [14]. The second one described a cutaneous metastatic melanoma where the patient noticed initial vision acuity decrease during pembrolizumab therapy. Fundus revealed atypical chorioretinal scars and pigment clumping [15]. This suggests that with our patient treated with pembrolizumab, intraocular corticosteroid injections might have controlled her MAR.

Conclusion

To our knowledge, we report the first case of MAR with a favorable outcome despite anti-PD-1 therapy being continued. Our patient benefited concomitantly from intravitreal injections of dexamethasone. This case encourages such a therapeutic alternative in patients with MAR requiring the use of ICI.

This case demonstrates that a close cooperation between ophthalmologists and dermatologists in charge of melanoma patients is crucial.

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Author's contribution Conception and design study were done by LP and BG. Acquisition and analysis of data, drafting the manuscript or figures, and final approval of the version to be published were performed by LP, QS, FM, BG, IM, and ADT.

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Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statement on the welfare of animals This article does not contain any studies with animals.

Informed consent Informed consent was acquired from the patient.

Conflict of interest The authors have no conflicts of interest, financial or material support to report.

Consent to participate Not applicable.

Consent for publication Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

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