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Case report

Melanoma-associated retinopathy

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ABSTRACT

A 63-year-old Taiwanese man with a history of cutaneous melanoma presented with a rapid onset of bilateral shimmering light and blurred vision. A fundoscopic examination was normal. However, visual field examination indicated generalized depression in both eyes. Scotopic rod-specific electroretinography (ERG) was undetectable and scotopic maximal combined-cone and rod-specific ERG showed the characteristics of negative ERG (a normal a-wave and a diminished b-wave, with the b-wave smaller than the a-wave), indicating dysfunction of the bipolar cells. Melanoma-associated retinopathy (MAR) was suspected and a systemic work-up gave a diagnosis of metastatic melanoma. This case shows the typical presentation of MAR. Greater awareness of MAR in patients with unexplained visual loss may help to identify an occult focus of metastatic melanoma.

1. Introduction

Paraneoplastic syndromes are caused by the immunological effects of a neoplasm located in a remote position away from the affected organ. Melanoma-associated retinopathy (MAR) is a paraneoplastic retinal disorder occurring in patients with cutaneous melanoma. Other paraneoplastic syndromes associated with vision loss include cancer-associated retinopathy, paraneoplastic optic neuropathy, and bilateral diffuse uveal melanocytic proliferation.

MAR was first reported and suggested to be a paraneoplastic phenomenon by Berson and Lessell,[1] who reported a night blindness syndrome in a patient with a pre-existing diagnosis of cutaneous melanoma. MAR has a sex ratio of 4.5:1 skewed towards men. Most patients only present years after the primary diagnosis of melanoma. The average latency from diagnosis of melanoma to recognition of MAR is 3.6 years.[2] Patients typically develop a sudden onset of flickering shimmering lights that begins from months to years after the diagnosis of melanoma. They often report night blindness, progressive loss of vision, and visual field constriction.[3] Ophthalmoscopic findings are usually minimal, although retinal pigment epithelial irregularity, retina arteriolar attenuation, and optic disc pallor have been reported. MAR is characterized by electronegative electroretinography (ERG) and dysfunction of the ON response bipolar cells, which is similar to the pattern in congenital stationary night blindness.

The incidence of melanoma varies worldwide, with a higher prevalence in highly pigmented individuals. Malignant melanoma is very rare in the Taiwanese population, with an incidence rate of 0.65/100,000.[4] To our knowledge there has been no previous report of MAR in Taiwan. We present here the case of a patient with MAR syndrome together with the corresponding electrophysiological measurements.

2. Case report

A 63-year-old Taiwanese man presented at our hospital in December 2011 reporting a rapid onset of blurred vision in both eyes. In addition, he reported shimmering light, poor side vision, and diminished visual acuity in low light environments. A general review indicated a previous history of cutaneous malignant melanoma on his left forefoot, with a Breslow thickness of 4.24 mm and a Clark level IV, which was first diagnosed in May 2009. A previous computed tomography scan gave negative results for metastatic disease. The wide local excision showed clear surgical margins and sentinel node biopsy was declined.

An ophthalmic evaluation showed that the best corrected visual acuity was 20/20 in the right eye and 20/28 in the left eye. A slit lamp examination, intraocular pressure, and fundus examination were all normal for both eyes (Fig. 1). The Humphrey field analyzer showed marked generalized depression in each eye (Fig. 2). Fluorescein angiography was normal, except for dye leakage on the left optic disc (Fig. 3).

Conflicts of interest: All authors declare no conflicts of interest.

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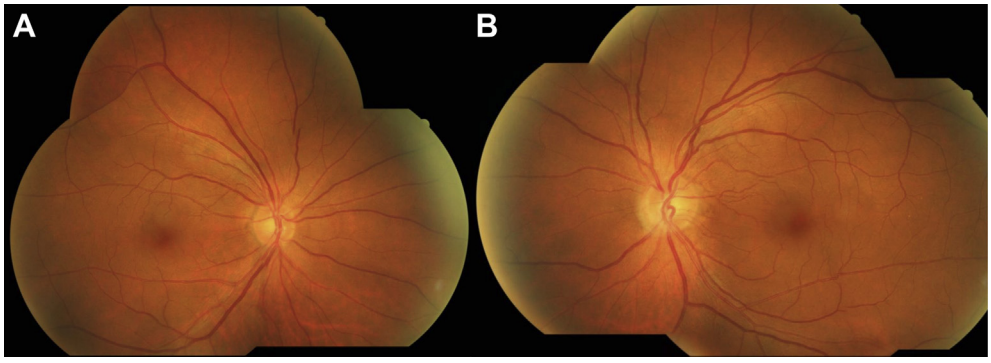

Fig. 1. (A,B) Fundus photographs of a patient with melanoma-associated retinopathy. The fundi appear normal in both eyes.

The scotopic rod-specific ERG was undetectable. The scotopic maximal combined-cone and rod-specific ERG showed an electronegative waveform in which the a-wave was normal, indicating normal phototransduction. The b-wave was so markedly reduced that the b-wave was smaller than the a-wave, suggesting dysfunction of the bipolar cells. The photopic ERG had a broad a-wave followed by a b-wave and lacked photopic oscillary potentials. The results of the long-duration ON–OFF ERGs showed a normal a-wave, a selectively diminished ON b-wave, and a preservation of the OFF d-wave, which further confirmed the involvement of depolarizing ON-bipolar cells (Fig. 4).

An initial diagnosis of MAR was considered. Full-body computed tomography and positron emission tomography scans showed local recurrence with regional, distant lymph nodes, liver, and bone metastases (Fig. 5). The patient began a course of biochemotherapy with interleukin 2 and dacarbazine in December 2011.

ERGs and visual field examination recorded 3 months after biochemotherapy treatment showed no significant change from the initial results. During the final visit in February 2012, visual acuity was correctable to 20/25 in the right eye and 20/50 in the left eye. Spectral domain ocular coherent tomography showed a normal retinal structure (Fig. 6).

3. Discussion

Early diagnosis of MAR can be difficult as a result of subtle clinical findings. ERG is extremely sensitive in detecting abnormalities associated with MAR. In ERG, a negative waveform (a-wave) represents the response of the photoreceptors, followed by a positive waveform (b-wave) generated by a combination of cells in the Müller/bipolar layer. MAR is characterized by an electronegative waveform, with a normal a-wave and a selectively reduced b-wave resulting in a b/a ratio of <1.0. These ERG changes imply dysfunction of the second-order neurons.[5] The rod-specific and cone- specific a-wave amplitudes and implicit times are relatively normal, which reflects a normal photoreceptor function.

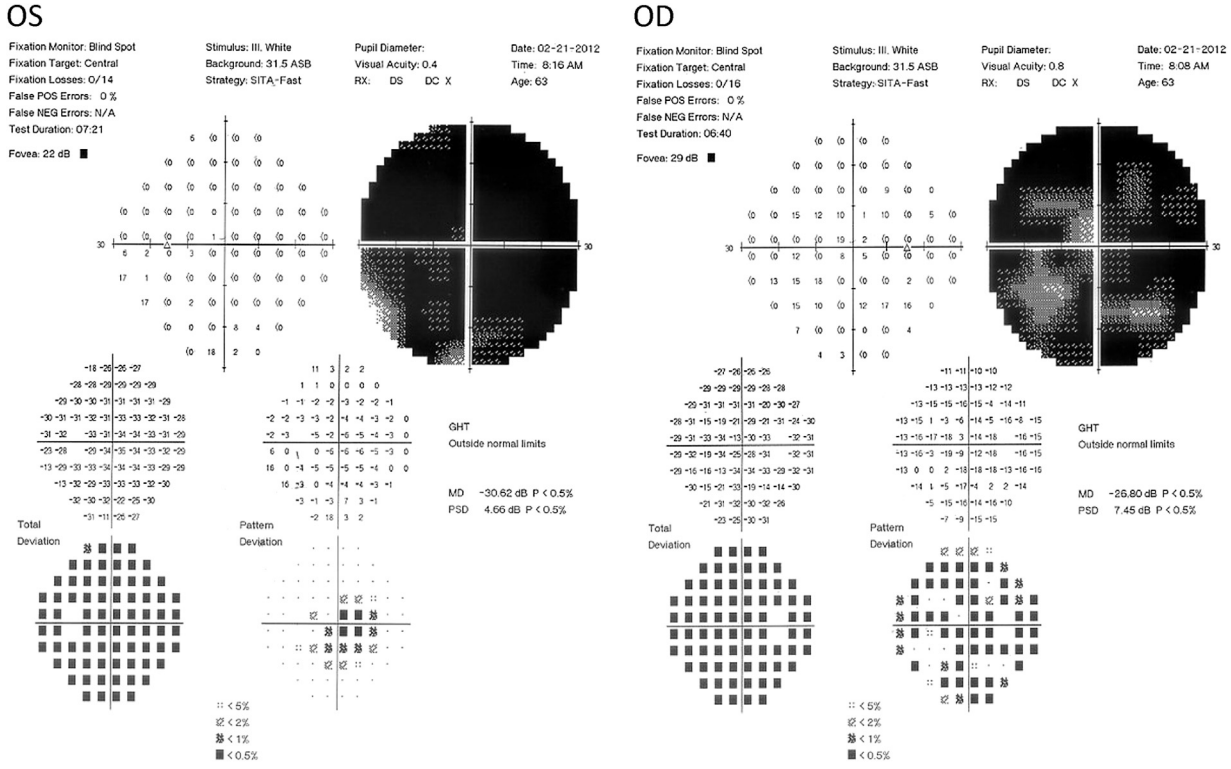

Fig. 2. Perimetric findings in a patient with melanoma-associated retinopathy.

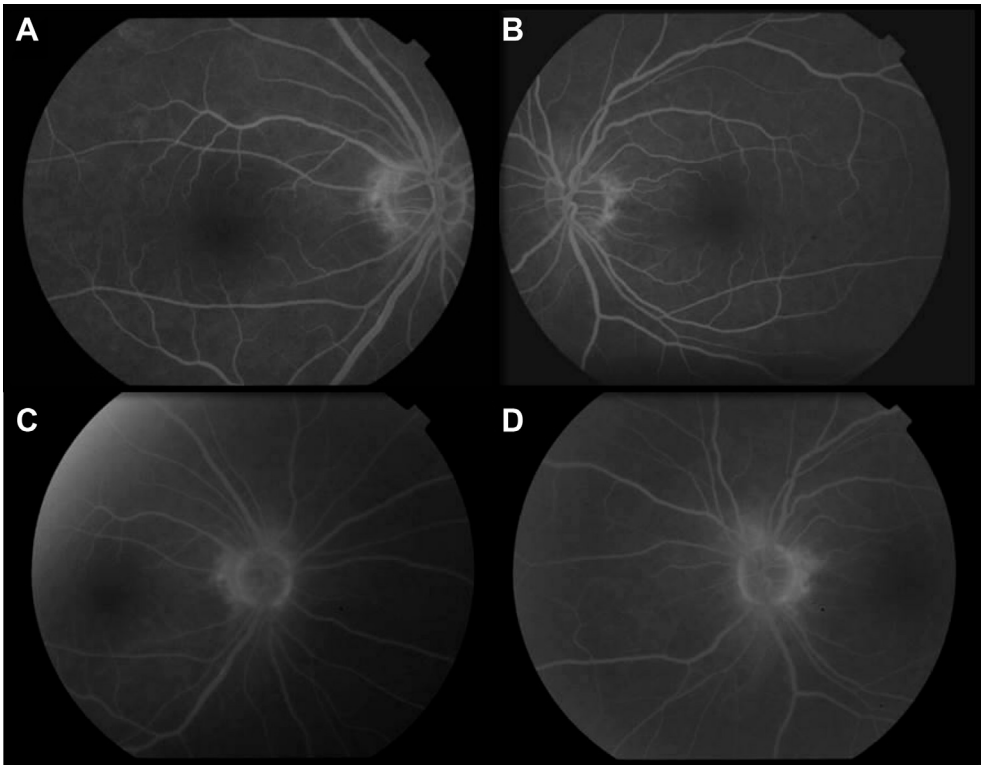

Fig. 3. The results from fluorescence angiography were normal (A,B) except for optic disc staining during the late phase (C,D).

After the phototransduction is complete, signals are transmitted from the photoreceptors to bipolar cells, and then to the ganglion cells. The normal cone b-wave responses consist of both ON and OFF components. The ON pathway transmits information relating to the onset of light, and the OFF pathway responds to the end of light stimulus. The depolarizing bipolar cells drive the ON pathway, and the hyperpolarizing bipolar cells drive the OFF pathway. In MAR, the ON pathway is selectively dysfunctional, but the OFF pathway is preserved. These changes may be caused by either dysfunction of the ON bipolar cells or by a defect in the synaptic

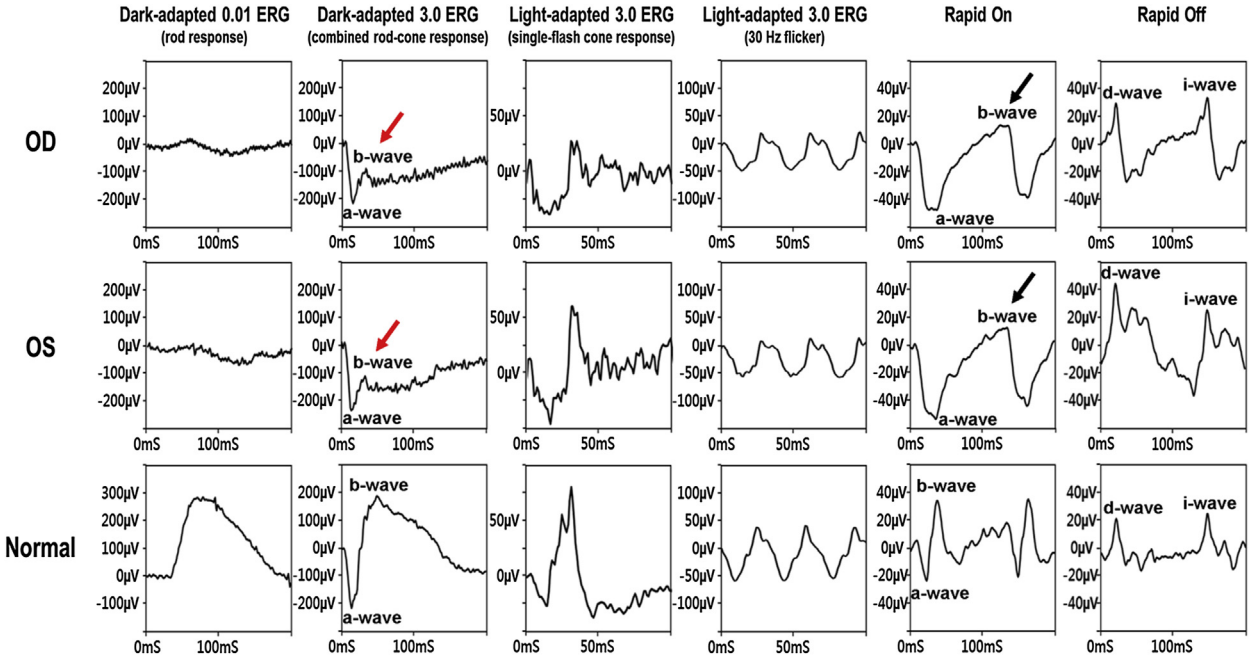

Fig. 4. Full-field standard electroretinograms (ERGs) and long duration ON–OFF ERGs. No scotopic rod response and a reduced b-wave amplitude with the shape of a negative ERG (red arrows) in scotopic maximal combined-cone and rod-specific response were noted in either eye. Normal a-wave, diminished ON b-wave (black arrows), and preservation of the OFF d-wave were present in long duration ON–OFF ERGs.

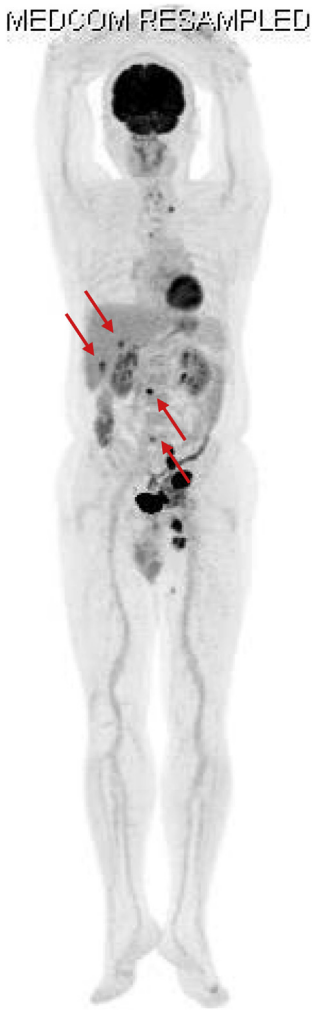

Fig. 5. Positron emission tomography whole body scan. The scan showed local disease recurrence with regional, distant lymph nodes, liver, and bone metastases (arrows).

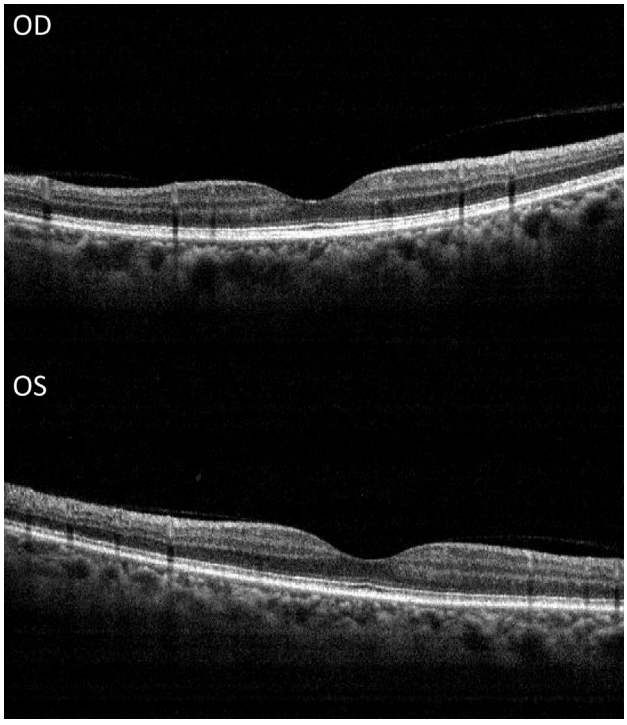

Fig. 6. Spectral domain ocular coherent tomography showed an overall normal retinal structure.

transmission between photoreceptors and depolarizing bipolar cells.[6,7] This is supported by the study of Lei et al,[8] which shows that an intravitreal injection of human MAR immunoglobulin G implicates the functional disruption of retinal depolarizing bipolar cell signaling in a monkey model.

Although the pathological process remains poorly understood, MAR is thought to originate from a B lymphocyte response to the production of antibodies against an unknown melanoma antigen, which cross-reacts with retinal components, particularly bipolar cells.[9] A previous study showed a strong family history of autoimmune disorders in most patients.[10] Examinations of serum for antiretinal antibodies by Western blot and indirect immunohistological investigations for a retinal inner nuclear layer and bipolar cell staining have given evidence for this theory, although the specific antibodies involved in MAR have not been systemically examined.

Diagnosing MAR is challenging because of its rarity and subtle ophthalmoscopic findings. In addition, the absence of a history of melanoma cannot rule out MAR because MAR may precede or follow the diagnosis of melanoma, and is not always associated with metastatic disease. Unexplained visual loss is a common reason for referrals of patients to visual function diagnostic laboratories. In this patient, we made the diagnosis mainly by ERG findings and clinical history. Unfortunately, we did not perform the serum test for antiretinal antibodies, nor immunohistochemistry to confirm the diagnosis.

Decreasing the tumor burden by cytoreductive surgery and adjuvant immunotherapy may result in the elimination of the associated antiretinal antibodies and the improvement of retinal function. There are concerns, however, that immunomodulatory treatment may increase the rate of death from cancer because patients with MAR may have antibodies that protect against the spread of tumors. However, Keltner et al[2] reported no difference in survival rates between treated and untreated patients. In addition, local periocular steroid treatment may improve visual function by stabilizing the outer retinal dysfunction from the autoantibodies, although the number of cases reported is limited.[11] Other treatments, including systemic steroids and plasmaphoresis, have also been reported to improve visual symptoms, but the long-term effects still need to be determined. Our patient was treated with interleukin 2 and dacarbazine biochemotherapy, but the results from ERG, visual field examination, and his vision showed no significant change 3 months after treatment.

Electrodiagnostic tests remain pivotal to objectively evaluate retinal function in the diagnosis of MAR. Serum testing for antiretinal antibodies and indirect immunohistological investigations can further confirm the diagnosis. Full-body imaging should be performed in suspected cases of MAR. Despite the rarity of this syndrome, it is important to have a greater awareness of its association with MAR to allow timely diagnosis and the treatment of future patients.

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