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CASE REPORT

Cancer-associated retinopathy (CAR) with electronegative ERG: a case report

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Abstract Cancer-associated retinopathy (CAR) should be suspected in patients who present with visual symptoms such as rapid unexplained visual loss and seeing shimmering lights, with an abnormal ERG. Electronegative ERG responses are not exclusive to melanoma-associated retinopathy (MAR) but may be seen in CAR as well. We describe a patient with CAR who presented with an electronegative ERG. A 67-year old woman, who presented with complaints of seeing shimmering lights, underwent an extensive ophthalmological and electrophysiological examination. Best-corrected visual acuity was 7/10 in the right and 9/10 in the left eye. Goldmann visual fields showed relative central scotomata and concentric narrowing. Slit-lamp and fundus examination were normal as was fluorescein angiography. Rod-specific ERG responses were severely reduced, with electronegative maximal combined rod-cone responses and delayed cone-responses with normal amplitudes. Melanoma-associated retinopathy was suspected. Extensive dermatological and internal evaluation eventually revealed an oat-cell carcinoma in the right lung. The patient died of pneumonia 2 years after presentation.

Keywords Cancer-associated retinopathy · CAR · Electronegative · ERG · Lung carcinoma · Melanoma-associated retinopathy

Abbreviations

CAR	Cancer-associated retinopathy
DBCs	Depolarizing bipolar cells
ERG	Electroretinogram
HBCs	Hyperpolarizing bipolar cells
MAR	Melanoma-associated retinopathy
PNS	Paraneoplastic syndromes

Introduction

Paraneoplastic syndromes (PNS) are an extensive group of clinical conditions that occur in patients with cancer, and result from mechanisms other than metastasis, metabolic and nutritional deficits, infections, coagulopathy and the side-effects of cancer treatment. The symptoms may be endocrine, neuromuscular or musculoskeletal, cardiovascular, cutaneous, hematologic, gastrointestinal, renal, or miscellaneous in nature. Most PNS result from immunological mechanisms triggered by the

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expression of proteins by the tumour, e.g. neurological proteins. Such immune responses are often induced by antibodies which react with the tumour and the nervous system, including the retina [1].

PNS associated with visual loss are rare diseases, with subtle but specific features that may be missed by the unsuspecting observer. Many patients present with visual symptoms, before the primary malignancy is diagnosed. It is therefore important for practicing clinicians to be familiar with these syndromes in order to allow early diagnosis of the disease and the underlying malignancy [2].

Two types of retinopathy are known to be associated with patients with malignancies: cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR) [3, 4]. CAR was first described by Sawyer and coworkers in 1976 [5]. The prevalence of this disease is unknown, with less than 100 cases reported in the literature [3]. MAR was first described in 1988, by Berson et al. [6]. It is less frequent than CAR [3]. CAR is most commonly associated with small-cell carcinoma of the lung, but it has also been less frequently reported in patients with breast, endometrial, and other cancers [7]. MAR has been described only in association with cutaneous malignant melanoma, and not with melanomas affecting other tissues [8, 9]. Unlike CAR, which usually heralds the onset of a malignancy, MAR commonly presents after the melanoma is diagnosed, often at the metastatic stage [3].

The clinical presentation of patients with CAR and MAR is rather similar. Symptoms at presentation include bilateral visual loss, photopsias, night blindness and photophobia. Clinical examination reveals abnormal visual fields and an apparently normal fundus in early stages, colour vision impairment and a prolonged dark adaptation.

Unlike the similar clinical presentation, the ERG pattern in CAR and MAR is different. In CAR, scotopic and photopic a- and b-waves are either absent or severely abnormal. However, maximal combined rod-cone ERG responses in MAR are electronegative.

We describe a patient whose electrophysiological presentation was suggestive of MAR, but the underlying malignancy turned out to be a carcinoma. To the best of our knowledge, this is the first report documenting an electronegative ERG in a patient with a CAR.

Case report

A 67 year-old woman first presented to our university hospital because of flickering photopsias of 4 months duration in both eyes. Her medical history included a colectomy 8 years before, for a moderately differentiated caecal adenocarcinoma. No positive lymph nodes were detected, and there was no indication for adjuvant chemotherapy. She had been smoking three cigarettes a day for several years, with the exact number of packyears unknown. Her medication consisted of clopidogrel and citalopram.

Best-corrected visual acuity was 7/10 (9/10 pinhole) in the right eye, 9/10 in the left eye with reading vision of Parinaud 1,4 in both eyes. The Amsler test was normal. Slit lamp examination, intraocular pressure and fundus examination were unremarkable in both eyes. An ISCEV-standard full-field flash electroretinogram showed a severely reduced scotopic b-wave, an electronegative maximal response, a delayed cone-specific a- and b-wave and a slightly delayed 30 Hz flicker (Fig. 1). An initial diagnosis of MAR was entertained, with CAR a less likely option. The patient was examined for a recurrence of colon cancer, but colonoscopy was normal. Further exhaustive internal and dermatological examination neither showed evidence of a carcinoma nor of a melanoma.

Two months after presentation the patient complained of bilateral loss of vision and an increase of photopsias (Fig. 2). However, best-corrected visual acuity was 9/10 in the right eye and 8/10 in the left eye. Amsler test, slit lamp and fundus examination remained normal. Goldmann visual field testing showed concentric constriction of the isopters and a relative central scotoma in both eyes, and a nasal step in the right eye. Colour vision testing was performed using the pseudo-isochromatic Ishihara (13 plate version), American Optical Hardy-Rand-Rittler and tritan plate tests, as well as the Farnsworth Panel D-15 test. A red/green defect and a medium blue/yellow defect was detected in both eyes. Contrast sensitivity was reduced for all frequencies in both eyes. The ERG was very similar to the preceding one. Fluorescein and indocyanine green angiography were unremarkable.

The constellation of ophthalmic findings in this patient was consistent with a diagnosis of MAR.

However, three months after presentation, an oat cell carcinoma of the lower lobe of the right lung was diagnosed, with positive mediastinal lymph nodes

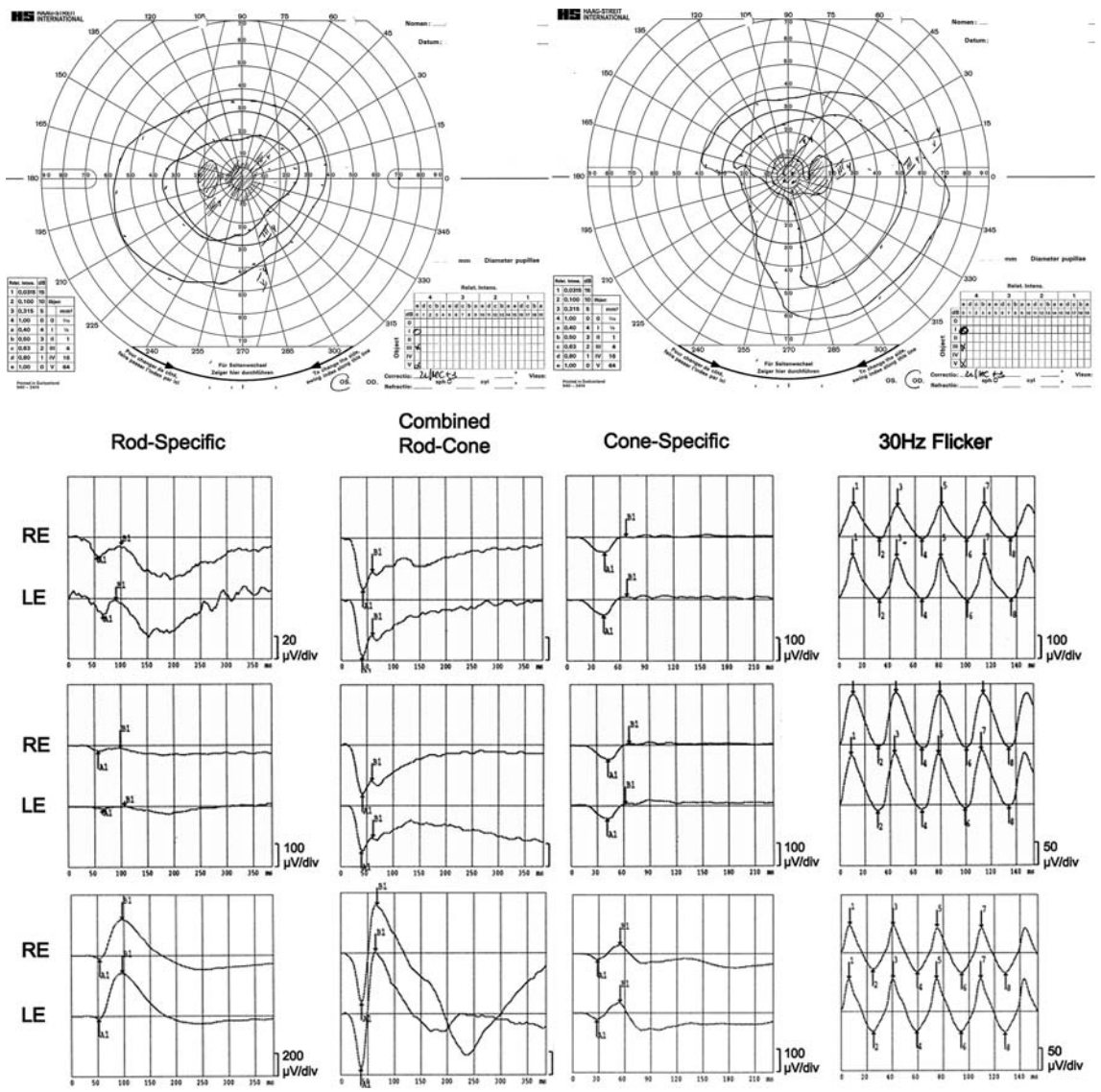

Fig. 1 Top left: Goldmann visual field of left eye; note moderate concentric constriction with relative central scotoma and generalised sensitivity loss Top right: Goldmann visual field of right eye with slightly less concentric constriction but more prominent inferonasal dropout and with relative central scotoma Bottom: ISCEV-standard full-field flash electroretinography (ERG) Top traces: ERG at presentation; note severely reduced rod-specific responses, electronegative combined rod-cone response, delayed cone-specific a- & b-wave, and slightly delayed 30 Hz-flicker responses Middle traces: virtually identical ERG findings 2 months after presentation Bottom traces: traces from normal subject for purposes of comparison

(TNM classification stage III). Chemotherapy was instituted. The patient died seventeen months later of pneumonia complicated by respiratory insufficiency. Although she was lost to ophthalmologic follow-up since she was diagnosed with lung cancer, visual function had improved slightly in the last months of life, according to her general practitioner.

Discussion

CAR and MAR are rare paraneoplastic retinal diseases with a rather similar clinical presentation, but different ERG patterns.

CAR patients present with subacute bilateral visual loss over several weeks to months. In half of

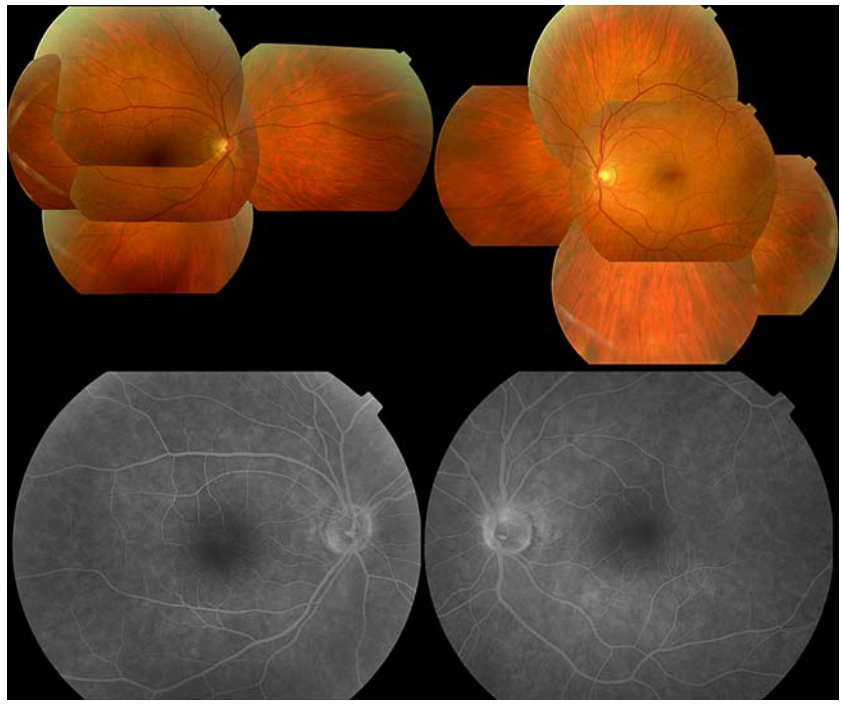

Fig. 2 Top left: fundus of right eye at presentation without any obvious abnormalities Top right: fundus of left eye two months after initial presentation, without any obvious abnormalities Bottom: normal late stage fluorescein angiogram of right eye (left) and left eye (right)two months after initial presentation

the cases, visual symptoms precede the diagnosis of the underlying malignancy by weeks or even months. Patients complain of positive visual phenomena of shimmering or flickering lights. Both eyes are affected, although not always simultaneously. The subacute progressive loss of central vision, colour vision impairment, glare, photosensitivity and central scotoma are attributed to cone dysfunction [2]. Night blindness, prolonged dark adaptation and field loss (generalized depression, arcuate scotomas, ring scotomas or extreme constriction of the fields) are due to additional rod involvement [2]. In MAR, patients frequently have an established diagnosis of cutaneous melanoma and develop visual symptoms years later, usually associated with nonocular metastasis [10]. The average delay of onset of visual symptoms from the time of diagnosis of melanoma is 3.6 years [2]. Patients frequently describe the sudden onset of a sensation of flickering light and night blindness, with subsequent progressive visual loss over several months [10–15]. In early stages of disease, the fundus may appear normal in patients with CAR or MAR. As the disease progresses, the retinal vasculature becomes attenuated, the optic discs appear pale and a thinning and mottling of the retinal pigment epithelium may be seen. Signs of retinal vasculitis and vitreous cells have been reported, usually in the later stages of disease [3, 4, 8, 9, 16].

CAR is characterized by clinical, histopathologic, and electrophysiologic evidence of degeneration and loss of both rod and cone photoreceptors, with ERG a-waves and b-waves markedly reduced in amplitude. However, selective cone dysfunction has been described [17].

On the other hand, the typical ERG pattern in MAR is an electronegative ERG. This is a selective reduction in amplitude of the b-wave, such that it does not exceed that of the a-wave [18]. Rod- and cone-specific a-wave amplitudes and a-wave implicit times are normal, which reflects normal photoreceptor function [2]. Dark-adapted combined rod-cone responses show a selective reduction in b-wave amplitudes, b-wave implicit times that are slightly shorter than normal, and an absence of oscillatory potentials [2, 11]. Light-adapted cone responses show a selective reduction in b-wave amplitudes, b-wave implicit times that are slightly longer than normal and reduced oscillatory potentials [2, 11]. Normal cone b-wave responses consist of both ON- and OFF-components [11]. The depolarizing bipolar cells (DBCs) drive the ON-pathway and the hyperpolarizing bipolar cells (HBCs) drive the OFF-pathway.

Both DBCs and HBCs subserve the cone pathways. Rods only connect to DBCs [17]. The ON- and OFF-components of the cone b-wave progressively become more separated with longer flash durations [11]. With a long-duration flash, the cone ON-component of the b-wave is lost but the OFF-component is preserved in patients with MAR [2].

The ERG changes either imply the dysfunction of second-order neurons (bipolar cells) of the ON-pathway, or a defect in the synaptic transmission between photoreceptors and DBCs [2].

In general, diseases that affect the inner retina, but spare photoreceptor function, manifest a negative ERG. Typical causes apart from MAR include: X-linked juvenile retinoschisis, congenital stationary night blindness, central retinal artery occlusion, birdshot chorioretinopathy, ocular siderosis, quinine toxicity, Oregon eye disease, Duchenne muscular dystrophy, Oguchi disease, vincristine-induced retinotoxicity and Batten disease. There have been isolated reports of negative ERG in patients with methanol toxicity, bull's eye macular dystrophy and Åland Island eye disease (Forsius-Eriksson syndrome) [18].

The selective attenuation of the b-wave of the rod-specific and combined rod-cone ERG, and the abnormal cone ERG ON-responses in MAR are similar to the ERG changes observed when L-2-amino-4-phosphonobutyrate is injected intravitreally into the monkey eye. L-AP4, a glutamate analogue, blocks signal transmission from photoreceptors to DBCs [19].

In MAR, the dysfunction of the bipolar cells leading to the electronegative ERG is caused by the production of antibodies that react against bipolar cells, probably of the depolarising type [20]. Immunohistochemical analysis show that antigens are located within the bipolar layer, where horizontal and amacrine cells intermingle with axons of Müller cells. The antigens involved are either small quantities of proteins, proteoglycans, lipids or carbohydrates [2, 10, 14]. Keltner et al. reviewed the clinical and immunologic findings of 62 MAR patients, and found that all patients produced autoantibodies reactive to components of the bipolar layer [10]. However, additional variations in immunologic features were apparent in those examined and involved a variety of different retinal cell populations in addition to the bipolar cells, including the optic nerve, nerve fiber layer, and photoreceptors. The specific bipolar cell antigens on which the antibodies react remain unknown. Antibodies against a 22-kd neuronal antigen (found in the retina but not in the optic nerve), a novel membrane-associated 33-kd protein, a 35-kd retinal Müller cell protein, and transducin have been demonstrated in some MAR patients [10, 15]. Ladewig et al. suggested there may be a correlation between the incidence and intensity of positive staining with stage of disease of the melanoma [21]. Follow-up studies will determine if patients with antiretinal antibodies go on to develop MAR [21]. It is clear that the variety of retinal antigens involved in indirect immunohistochemical staining and Western blot analysis strongly suggests that several antigens, shared by the retina and the neoplasm, may be involved [10].

The patient presented here had an electronegative maximal rod-cone ERG, and a delayed a-wave implicit time of cone-specific responses. An electronegative maximal rod-cone ERG suggests bipolar cell dysfunction, which is somewhat surprising as she was diagnosed with a primary lung carcinoma rather than a skin melanoma. In contrast, the delay in a-wave implicit time of cone-specific responses suggests photoreceptor involvement, which is different from what is traditionally noted in MAR.

It may be that the patient had produced antibodies against bipolar cells and, to a lesser extent, against cone photoreceptor cells. Indeed, anti-bipolar cell antibodies have been demonstrated by Jacobson and Adamus in a patient with CAR, which suggests that autoantibodies to retinal bipolar cells may be found in more than one paraneoplastic retinopathy [22]. In addition, anti-bipolar antibodies were also found in patients without apparent malignancy [2]. The patient described by Jacobson and Adamus, had absent ERG responses of the right eye and decreased responses of the left eye, especially those under scotopic conditions, which eventually improved after treatment [22]. In contrast, our patient has an electronegative ERG. Unfortunately we were unable to analyse the presence of antiretinal antibodies in our patient.

Numerous antigens have been reported to be associated with CAR also: recoverin (23-kd), α-enolase (46-kd), heat shock cognate protein (65-kd), 20–26, 34, 45, 48, 60, 70, 145, and 205 kd, tubby-like protein-1, photoreceptor cell-specific nuclear receptor gene product, neurofilaments, retinal ganglion cells

and retinal bipolar cells [23]. A retrospective review of 18 patients with CAR showed that recoverin was found in 100%, although only in 60% were these identified at the initial examination, with the remainder becoming apparent on subsequent testing [24].

In addition, different antibodies can be associated with different clinical presentations and ERG patterns. Indeed, there is a phenotypic difference between patients with CAR who either have antirecoverin or antienolase antibodies [25, 26]. Dot et al. describe a patient with small cell lungcarcinoma whose serum tests showed antiretinal protein 35-kd before surgery, antiretinal protein 35-kd and 46-kd (α-enolase) 1 week after surgery, and anti-α-enolase 1 month after surgery. The phenomenon of new antibodies emerging during the course of disease suggests "epitope spreading", which refers to the development of an immune response to epitopes distinct from, and non cross-reactive with, the initial disease-causing epitope. Epitope spreading enhances heterogeneity and pathogenicity of the antibodies in CAR [25]. Anti-α-enolase antibodies can also be found in autoimmune retinopathy, and a number of inflammatory, degenerative, and neurologic diseases, even in patients with glaucoma and in healthy subjects. Anti-enolase antibodies may label several layers and cell types within the retina, whereas antirecoverin antibodies bind almost exclusively to rods and cones and some bipolar cells [26].

To the best of our knowledge, this is the first patient reported with CAR and an electronegative ERG. This case illustrates that electronegative ERG responses are not exclusive to MAR, but may be seen in CAR as well.

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