Severe course of cutaneous melanoma associated paraneoplastic retinopathy

Ulrich Kellner, Norbert Bornfeld, Michael H Foerster

Abstract

Background—Melanoma associated retinopathy (MAR) is a paraneoplastic syndrome in metastatic cutaneous melanoma presenting with nightblindness, light sensations, mild visual loss, and reduced b-waves in the electroretinogram (ERG).

Methods—A patient with MAR was followed for a period of 25 months with repeated examinations including visual field testing and recording of standard electro-oculography, standard ERG, and photopic On and Off responses.

Results—A male patient with a very severe course of MAR is described. In addition to the clinical signs seen in previous patients, severe visual deterioration and vitreous inflammation were the predominant signs. The vitreous inflammation resolved after systemic corticosteroid therapy. Nightblindness and the reduced b-waves in the ERG remained unchanged during the follow up period. However, further visual deterioration and paracentral scotomas developed. Dark adaptation was markedly abnormal. Photopic On responses were reduced, but Off responses were preserved. Antibodies against retinal bipolar cells were isolated from blood samples of this patient.

Conclusion—Vitreous inflammation may mask the diagnosis of MAR. ERG findings indicate that the most severe and progressive course is the result of local retinal changes and not progressive generalised retinal degeneration.

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Since the report by Sawyer et al, several patients with retinal degenerations associated with extraocular tumours have been described. Cancer associated retinopathies (CAR) can be distinguished from cutaneous melanoma associated retinopathies (MAR) both clinically and immunologically. CAR patients present with severe visual loss including complete blindness and severe reduced a- and b-wave amplitudes in the electroretinogram (ERG).2–6 Autoantibodies reacting with photoreceptors and ganglion cells have been isolated from the blood sera of CAR patients.3 7–13

The cases of 16 MAR patients have been described in the literature to date.14–25 Symptoms included mild visual loss, nightblindness, and shimmering or flickering light sensations; a b-wave reduction was observed in the ERG. This ERG waveform, called a ‘negative ERG’, can be found in disorders affecting neuronal transmission pathways beyond the photoreceptors or other cells within the inner retinal layers.26–29 Autoantibodies reacting with retinal bipolar cells have been isolated from blood sera of all MAR patients examined.23 25 30 Only one patient with a metastatic carcinoma developed signs similar to MAR.31 In contrast with previously reported patients with MAR, the male patient described in the present study showed progressive visual loss and signs of posterior uveitis.

Methods

ELECTRORETINOGRAPHY

A negative ERG was first recorded in this patient in August 1992. Thereafter, the recording equipment was changed. For comparison during follow up, only ERG recordings with the new equipment were evaluated. The new technique corresponds to our technique described previously.28 29

The ERG recording protocol includes all recordings according to the standard for clinical electroretinography.32 A Nicolet Spirit (Nicolet, Madison, USA) in combination with a Nicolet Ganzfeld was used for stimulation and recording. Recordings were done after 30 minutes of dark adaptation and with maximal dilated pupils (2.5% phenylephrine and 0.5% tropicamide). Stimulus duration was 0.1 ms. Four stimuli were used for recordings in the dark. The maximum light intensity was 10 cd s/m². Duration of light adaptation before recording was 10 minutes. Light adapted recordings were performed in the presence of white light adaptation of 30 cd/m² with white and chromatic stimuli of maximum light intensity. Kodak Wratten filters were used for white chromatic stimuli (blue: No 47 + 47A + 47B, maximum transmission at 445 nm, green: No 61, 538 nm; red: No 29, 630 nm). No averaging was done.

ON/OFF RESPONSES
On and Off responses were recorded using red light emitting diodes (LEDs) (3 cd m²) and flashes of long duration (256 ms). Recordings were done after 10 minutes of light adaptation (10 cd/m²). Eight responses were averaged. The method has been described in detail by others.33 34

ELECTRO-OCTULOGRAPHY
Electro-oculography (EOG) was performed using a method described by Behrens et al35 and according to the standard for clinical EOG.36 A Ganzfeld with fixation lights was
used for stimulus presentation and induction of eye movements. The duration of measurement was 56 minutes. Within the first 40 minutes, the luminance was decreased monotonically by four decades (2000 to 0.2 asb) in a logarithmic manner to become independent of the previous state of adaptation. After this adaptation procedure, a luminance step of four decades induced the light rise. The potentials were recorded with a DC amplifier. The response was described by the ratio between the maximum amplitude to the amplitude before the luminance was increased (light peak versus baseline).

**DARK ADAPTATION**

Dark adaptation was tested with the Goldmann-Weekers adaptometer. After a 10 minute bleach of 1400 cd/m² in a Ganzfeld sensitivity thresholds were determined over a period of 45 minutes.

Clinical history

The clinical history of this 44-year-old man began in April 1989 when he presented with a cutaneous melanoma of the left leg. This lesion was locally excised and the patient was treated with systemic interferon. In March 1990, a local lymph node metastasis was excised; no further medical treatment was given. Regular follow up examinations during the next 4 years revealed no further evidence of metastatic disease. The patient was otherwise in good health with no personal or family history of eye disease. He denied difficulties with seeing at night or with colour vision before 1991.

In January 1991, the patient noted for the first time difficulties in seeing at night as well as a deterioration of visual acuity in the right eye. An overview of the ophthalmic findings by this and subsequent presentations is summarised in Table 1. Two to 3 weeks later, visual loss occurred in the left eye. A visual loss of unknown cause was diagnosed elsewhere.

**Table 1: Summary of clinical findings**

<table>
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<th>Date</th>
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<th>Visual fields</th>
<th>Vitreous haz (both eyes)</th>
<th>Fundus findings</th>
<th>Treatment</th>
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**Figure 1**

Ophthalmoscopic findings in MAR. Vitreous haze reduced visibility of the posterior pole in August 1992 (A) right eye, (B) left eye. In November 1993 fundus visibility was good (C) right eye, (D) left eye. On the right eye the paracentral scotoma and the scar temporal to the optic disc were enlarged compared with August 1992.
June 1991, uveitis was diagnosed on the basis of an observed vitreous haze and cellular infiltration. Systemic corticosteroid treatment of unknown dosage led to an improvement of visual acuity.

One year later, the patient was referred to our department because of recurrent bilateral posterior uveitis. He complained of a further deterioration in visual acuity. On examination, the visual acuity was 6/12 in the right eye and 6/7-5 in the left. Anterior segments were normal in both eyes. Slit-lamp examination revealed vitreous haze and mild cellular infiltration in both eyes. In the right eye, there was a small scar located paracentrally and another one at the temporal side of the optic disc (Figs 1A and B). Otherwise fundoscopy was normal in both eyes. At that time antibody testing was negative for varicella zoster, herpes simplex, cytomegalovirus, rubella, borreliosis, and syphilis. Testing for toxoplasma antibodies (enzyme linked immunosorbent assay) was negative for IgM. A low positive IgG titre was found indicating a previous infection.

In August 1992, the patient's visual acuity dropped to 3/60 in the right eye and to 6/12 in the left. Goldmann visual fields showed concentric narrowing in both eyes (Figs 2A and B). The vitreous haze was more dense with increased cellular infiltration in both eyes. Oral prednisolone (initially 100 mg/day) with tapering over 4 weeks resulted in resolution of the vitreous haze and improvement in visual acuity to 6/36 in the right eye and to 6/7-5 in the left. At that time, the ERG showed reduced b-wave amplitudes. Pattern visual evoked cortical potentials revealed low amplitudes with normal P100-latencies in both eyes.

For the next 7 months the patient's visual acuity remained stable. In March 1993, however, the visual acuity decreased to 1/60 in the right eye. It remained unchanged with 6/12 in the left eye. Examination of visual fields showed a central scotoma in the right eye and paracentral scotomas in the left. Dark adaptation, measured with a Goldmann-Weekers adaptometer, was monophasic with a slow cone limb and no evidence for rod activity. Colour vision testing on the left eye revealed multiple errors on the desaturated Pasc D-15 test without typical axis of confusion. On the Nagel's anomaloscope, the range of matches was extended to the proton side. Systemic corticosteroid therapy (50 mg/day) improved vision subjectively, the patient describing his sight to be less hazy without the disturbance of flickering lights. Visual fields were also slightly improved; however, the visual acuity, ERG, and vitreous haze remained unchanged. Termination of corticosteroid therapy resulted in increased subjective discomfort. Consequently, treatment was recommenced.

In June 1993, visual acuity, visual fields, ophthalmoscopic findings, and ERG were
acuity improved after treatment with oral acetazolamide and local flurbiprofen. An attempt to discontinue this therapy resulted in recurrent visual loss within 10 days to 3 weeks. Consequently, the patient continued to receive the above regimen with few attempts at discontinuing to date. Upon examination in November 1993, visual acuity in the right eye increased to 3/60 and to 6/12 in the left. Visual acuity and visual fields remained unchanged in April and August 1994 (Figs 2C and D). Comparison of fundus photographs indicated that the scars in the right eye had slightly increased in size (Figs 1C and D). No other morphological changes were observed.

In April 1994, an EOG recording showed a reduction in the light peak versus baseline ratio: 127% in the right eye and 146% in the left one (normal 80%.). Four months later, the coloured caps of the desaturated Panel D-15 test could not be distinguished by the patient. He had much less difficulty in performing the Farnsworth 100 hue test with saturated colours. The total error score was 80, within the normal range. The main errors were found along the tritan axis.

**BLOOD EXAMINATION**

In May 1993, serum of the patient was sent to A H Milam, University of Washington, Seattle, where it was prepared and examined as described previously. Antibodies from this serum labeled rod bipolar cells similar to findings seen in other MAR patients (Fig 4). An examination of a second blood sample in October 1994 gave identical results.
Results

ELECTRORETINOGRAPHIC FINDINGS

At dark adaptation, the a-wave amplitudes were normal and the b-wave amplitudes were reduced at all stimulus intensities, showing a negative ERG (Figs 5, 6). At maximum stimulus intensity, the b-wave amplitudes were about one third of the normal value. At light adaptation, the configuration of the response was altered. The a-wave amplitudes were normal to white and chromatic stimuli and had a normal time course. The b-wave amplitudes were borderline; however, the b-wave latencies and implicit times were markedly delayed. The b-wave implicit time was 40 ms (range at repeated examinations 39–40.8 ms; white stimulus) in the patient compared with 32.6 (1.4) ms (mean 2 SD) in normals. The oscillatory potentials, seen as wavelets on the ascending limb of the b-wave in the normal response, were reduced to one small wavelet before the b-wave resulting in a broad negativity between the a- and the b-wave. The amplitude of the 30 Hz flicker response was subnormal.

In contrast with the clinical findings, the ERG findings were similar in both eyes (Fig 6). The ERG variables (amplitudes and latencies) showed only small changes during the course of the disease (Fig 6). They did not correlate with the variation of clinical findings (Table 1).

ON/OFF RESPONSES

In contrast with responses elicited with light flashes of short duration (0.1 ms, Fig 5), presentation of long duration flashes (250 ms, Fig 7) separates the b-wave into a positive On response at the beginning of the flash and a positive Off response at light cessation. The On response has been attributed to the depolarising cone bipolar cells and the Off response to the hyperpolarising cone bipolar cells.44 In the patient, the On response was severely reduced and the Off response was normal (Fig 7).

Discussion

To date, 16 patients with MAR have been described in the literature.14–25 It should be noted, that the patient described by Dubois et al19 was misdiagnosed initially and MAR was suspected later.17 The patients described by Kim et al22 and Wolff and Arden27,28 are identical.

Ophthalmic signs were found either before or during the development of metastasis of a cutaneous melanoma. All patients had sensations of shimmering lights, difficulties with night vision, and reduced b-wave amplitudes in the ERG. In contrast with the current case, visual acuity was usually normal or only moderately reduced (not below 6/12). Only one patient developed severe visual loss with central scotomas25 paracentral scotomas were seen in two patients. In most patients, colour vision remained unchanged. Ophthalmoscopic findings were normal in most cases, with a few vitreous cells being described in one patient only.23 The clinical courses showed progression of scotomas in one patient24 and were stable up to 14 months in two other patients.18,23

In the first MAR patient described, a side effect of vincristine therapy was suspected,14 however, findings in that patient were similar to others who did not receive vincristine.15,19,20–23 The patient described in this study did not undergo treatment with vincristine. Systemic treatment with interferon may induce a retinopathy characterised by cotton wool spots, areas of non-perfusion, and haemorrhage.35 Such alterations were not observed in our patient.

The patient described in this study developed a very severe course of MAR. In addition to the clinical signs reported in other MAR patients, our patient initially presented with ocular inflammation. This would explain the visual loss and visual field defects observed at that time. The posterior uveitis must be attributed to the paraneoplastic process. General history and immunological examinations revealed no indications for an unrelated cause of uveitis. The low IgG titre for toxoplasmosis is a sign of a previous infection. The clinical findings of bilateral uveitis without a localised chorioretinal inflammation would be
Figure 7 On and Off responses of our patient compared with representative normal recordings. Two independent recordings of one eye are shown for the patient and the normal person. Stimulus duration was 256 ms. The On response was markedly reduced in the MAR patient, but the Off response was preserved.

very atypical for ocular toxoplasmosis. The scar in the right eye enlarged during follow up without any signs of inflammation. During follow up examinations, the ocular inflammation gradually resolved and progressive visual loss and paracentral visual field defects occurred. Despite the difference in visual acuity, the ERG recordings were similar in both eyes. In contrast with the variable clinical course over the subsequent 20 months, little variation was observed in ERG variables. Therefore the visual loss and the paracentral scotomas detected in this patient could be attributed possibly to localised macular changes rather than to a progressive degeneration of the whole retina. One female MAR patient with severe visual loss has been reported recently. She presented with central scotomas, moderately pale optic discs, and severely attenuated retinal vessels. Fluorescein angiography for differentiation of macular changes were not performed. It is not known whether vitreous inflammation was present during the early course of disease. Similar findings were not seen in other MAR patients.

The antibodies against rod bipolar cells isolated from the blood serum of our patient were similar to those seen in every MAR patient examined so far (A Milam, personal communication). Similar antibodies could not be detected in other eye diseases or normals. The vitreous inflammation is consistent with the autoimmune mechanism of paraneoplastic retinopathy. An induction of vitreous inflammation has been demonstrated for several antibodies against retinal proteins.

In one MAR patient, fine vitreous cells were described. In other patients with metastatic cutaneous melanoma, anterior uveitis and a Vogt-Koyanagi-Harada syndrome have been observed. Nightblindness was also reported in one of these patients. The development of uveitic signs may depend on the severity of the autoimmune reaction directed against the bipolar cells (for example, a more severe breakdown of the blood-retinal barrier) or on individual variations in reactivity of the immune system. In our patient, ocular involvement started 9 months after diagnosis of a local metastasis. There was no indication that the recurrences of vitreous inflammation were associated with tumour activity elsewhere in the body. It has to be emphasised that the signs of inflammation delayed the correct diagnosis for approximately 1 year.

The ERG recordings in our patient and in other patients with MAR are in accordance with a defect of rod bipolar cells. When dark adapted, the a-wave amplitudes, indicating photoreceptor function, were normal. The b-wave amplitudes, indicating bipolar and Müller cell function, were reduced. The elevated thresholds at dark adaptation indicate a severe transmission defect in the rod pathway.

In our patient, the cone pathways were also affected. When light adapted, the b-wave amplitudes were borderline and the implicit times were prolonged. The 30 Hz flicker response was reduced. The On response was reduced and the Off response preserved in our patient (Fig 7). This has been described previously by Alexander et al and is evidence for a defect of the depolarising cone bipolar cells.

Similar ERG findings are seen in congenital stationary nightblindness (CSNB). MAR and CSNB have several features in common which may suggest that these diseases affect similar retinal structures. Some differences, however, indicate that MAR is not an acquired stationary nightblindness. For example, in contrast with patients with CSNB, the blue cones appear to be affected in MAR. Difficulties in detecting blue colours have been observed in our and other patients. Further, the blue cone ERG can be severely reduced in MAR patients. Extended psychophysical testing in two MAR patients revealed severe defects of the magnocellular pathway with preservation of the parvocellular pathways.

Our patient underwent similar psychophysical testing, the results of which will be presented in detail elsewhere (J Wolf and G Arden, in preparation). He had similar characteristics with achromatic low spatial frequency losses at low contrast corresponding to magnocellular losses. However, compared with the other MAR patients, he had greater losses in his achromatic high spatial frequencies, consistent with his reduced visual acuity (J Wolf and G Arden, personal communication). There are indications that the parvocellular and magnocellular pathways are separated on the level of the retinal bipolar cells. It has been demonstrated recently that only a subset of about 30% of bipolar cells is labelled with antibodies of MAR patients. One may speculate, that rod bipolar cells and cone bipolar cells of the magnocellular pathway express similar proteins which are not expressed by cone bipolar cells of the parvocellular pathways. Consequently, some bipolar cells could be more vulnerable to MAR antibodies than others. Two possible target proteins are protein kinase C and a G protein. In the cat, the G protein could be detected in rod bipolar cells and depolarising cone bipolar cells which carry low spatial frequencies, but not in other depolarising cone bipolar cells. A defect of the G protein could explain the functional findings seen in MAR patients.
We suppose that the course of MAR is initiated by circulating antibodies reacting with bipolar cells. This is reflected clinically by a rapid onset of the disease; for example, all MAR patients report a sudden onset of nightblindness. Although differences of onset between both eyes have been observed in our and other patients, it is not clear if this time difference was short and never longer than 2 months. Apparently a certain number of bipolar cells have to be affected before nightblindness becomes clinically obvious. It may be suggested that the retinal damage occurs during this initial phase followed then by a stationary phase. This is indicated by a non-progressive clinical course in most MAR patients. Repeated ERGs in our patient were unchanged indicating that no progressive retinal degeneration was present. The progressive deterioration of visual acuity in this case must be attributed to localised macular changes secondary to posterior uveitis.

It remains puzzling how antibodies against rod bipolar cells can induce defects in the cone pathways. Further analysis is necessary to determine the meaning of severely reduced cone b-waves and missing ON responses when photopic physiological data indicate preservation of important cone functions as good visual acuity, normal colour vision, and intact parvocellular pathways in most patients. The origin of the flickering light sensations also remains unknown. Detailed evaluation of MAR patients may reveal new insights into retinal circuitry in the future.

We thank Mrs H Kraus for help with the ERG recordings and Mr G Böskamp for fundus photography. Immunological examination of the blood serum was done by Professor A H Milam (Department of Ophthalmology, University of Washington, Seattle). Detailed psychophysical examinations were performed by Dr J Wolf (Department of Optometry and Visual Science, City University, London) and Professor G B Arden ( Moorfields Eye Hospital, London).
