A type of acquired night blindness can occur in association with cutaneous malignant melanoma. Characteristics of this disorder include a rapid onset of night blindness, a constant sensation of shimmering or pulsating light, dark-adapted thresholds that are elevated approximately 3 log units above normal, and a selective reduction in the amplitude of the b-wave of the dark-adapted electroretinogram (ERG). In one such patient, the double density of rhodopsin, rhodopsin regeneration kinetics, the rod a-wave, and the electro-oculogram were all normal, indicating normal functioning of the outer segments of the rod photoreceptor cells. These findings suggest that the visual abnormalities are probably a result of a defect in signal transmission between rod photoreceptors and second-order neurons.

Two different hypotheses have been proposed to account for the onset of visual symptoms in this condition. The first is that the visual dysfunction is the result of a neurotoxic effect of the drug vincristine sulfate administered as chemotherapy, possibly through disruption of the synaptic mechanism of photoreceptor cells. In support of this, vincristine application to the arterially perfused cat eye results in a selective attenuation of the rod b-wave similar to that observed in patients with this form of night blindness. Alternatively, it has been proposed that the syndrome is a paraneoplastic response to a metastatic cutaneous melanoma because visual symptoms apparently can occur without chemotherapy.

We describe our findings in a patient with cutaneous malignant melanoma without metastatic ocular lesions who developed visual symptoms comparable to those described in the two previous studies. The characteristic night blindness, sensation of shimmering light, and ERG abnormalities were present before vincristine administration, supporting the hypothesis that the condition is a paraneoplastic consequence of a malignant melanoma.

Abnormalities of the rod system observed in this acquired form of night blindness are similar to those found in patients with the “complete” form of congenital stationary night blindness (CSNB). Patients with CSNB also have alterations in the ERG b-wave of the cone system, including a reduction in cone b-wave amplitude.
wave amplitude\textsuperscript{5-9} and, in at least some patients, a prolonged cone b-wave implicit time.\textsuperscript{5,8,9} Recently, it was demonstrated that the cone b-wave abnormality in patients with CSNB results from a selective reduction in the "on" response component with relative preservation of the "off" response.\textsuperscript{5-11}

To determine whether there is a comparable cone b-wave abnormality in the acquired night blindness associated with a cutaneous melanoma, we compared the response properties of the cone system ERG in our patient with those of two patients with CSNB. We report that the patient with melanoma had a selective reduction in the "on" response component of the cone system ERG similar to that observed in the patients with CSNB, suggesting a common underlying defect.

**Materials and Methods**

**Patient**

Our patient was a 58-year-old man with documented metastatic cutaneous malignant melanoma. In 1975, a primary malignant melanoma was removed from the left side of his scalp. A radical neck dissection at that time revealed several positive cervical lymph nodes. On January 19, 1990, the patient first noticed floaters in his right eye. Approximately 2 weeks later, similar symptoms were observed in his left eye. About 3–4 weeks subsequently, he had problems seeing at night, which prevented driving. He also complained of annoying fields of shimmering light that fluctuated in brightness but never disappeared. He had served in the Korean War and did not have any night vision problems at that time.

The patient initially was seen in the Department of Ophthalmology at Loyola University (LU) Medical Center on January 26, 1990, for complaints of floaters and decreased visual acuity. On February 8, ERG recordings were obtained that showed reduced b-wave amplitudes under both dark-adapted and light-adapted conditions. On April 27, 1990, a metastatic mediastinal lesion was diagnosed at the Mayo Clinic. Beginning on June 7, 1990, he underwent chemotherapy that included vincristine sulfate, bleomycin sulfate, dacarbazine, and lomustine. During this treatment, vincristine sulfate was administered intravenously twice a week for 1 week. After chemotherapy was discontinued for 3 weeks, he again underwent similar treatment, receiving vincristine sulfate twice with the other medications during a 5-day period, for a total dose of 6 mg of vincristine sulfate. The patient was receiving atenolol (Tenormin; ICI, Wilmington, DE) for treatment of systemic hypertension and allopurinol for gout. In addition, he received tapering doses of oral prednisone over approximately 3 months, beginning with 80 mg/day in September 1990. No changes in the ERG were observed during this period.

The patient’s cornea, anterior chamber, lens, and vitreous were clear bilaterally, and his pupils reacted normally. Intraocular pressures were 14 mm Hg in the right eye and 13 mm Hg in the left. Fundus examination showed nonspecific pigment mottling in the posterior pole with a slight degree of vascular attenuation. The optic discs appeared normal. Visual acuity was approximately 20/25 in each eye. Refractive corrections were $-2.50 + 3.00 \times 120^\circ$ (in the right eye) and $-1.00 + 2.25 \times 70^\circ$ (in the left). Visual field testing with a Goldmann perimeter showed no evidence of a peripheral restriction to either a II4e or V4e target. No scotomas were apparent in the left eye; the right eye had an enlarged blind spot and a small parfoveal relative scotoma (II4e target). No significant changes in visual acuity or visual fields were evident approximately 14 months after the onset of visual symptoms.

The patient’s dark-adapted peripheral detection thresholds for a 500-nm test flash were elevated above the upper limits of normal by more than 3 log units, confirming a degree of night blindness in this patient consistent with previous studies of this condition.\textsuperscript{1,2} A comparison of detection thresholds for 500-nm and 656-nm test flashes indicated that thresholds for the 500-nm flash were rod mediated at eccentricities beyond 20°, similar to results found previously in two CSNB patients.\textsuperscript{12}

Our patient’s Rayleigh match range (41–43) on a Nagel Model I anomaloscope was normal,\textsuperscript{13} and his performance on the Farnsworth Panel D-15 test was also normal, with one minor cap transposition. However, on the Farnsworth-Munsell 100-hue test, he had a total error score of 388 (log error score, 2.6). According to a quadrant analysis,\textsuperscript{14} the errors fell along both red–green and blue–yellow axes, with a tritan axis predominating (difference score, +3.2). In addition, his foveal dark-adapted spectral sensitivity was reduced in sensitivity more for short and middle wavelengths than for long wavelengths.

**ERG**

Our patient’s ERGs were recorded at LU before chemotherapy (February 8, 1990) and at the University of Illinois at Chicago (UIC) on all other occasions (all done after he received chemotherapy). At both sites, strobe-flash ERGs were recorded with Nicolet (Madison, WI) Ganzfeld stimulators and Nicolet Compact Four signal averagers. Recording electrodes were Burian-Allen contact-lens electrodes, with the reference electrode either in the speculum (LU) or
attached to the forehead (UIC), and with the ear lobe grounded in both cases. The amplifier band-pass settings were 1–1000 Hz. Flash luminances were attenuated with internal strobe settings and Wratten neutral density filters (Eastman Kodak, Rochester, NY). Stimulus luminances at both test sites were calibrated with EG&G model 550 photometers (Princeton, NJ) equipped with luminance probes and flash integrators.

The pupil of the test eye was dilated with tropicamide 1% and phenylephrine hydrochloride 2.5% drops. After approximately 30 min of dark adaptation, the contact-lens electrode was inserted under dim red illumination, and dark-adapted luminance-response functions were obtained with white (xenon) flashes. These were presented in order of increasing luminance with a 15-sec interflash interval. Next, a rod-desensitizing adapting field of 1.5 (LU) or 1.3 (UIC) log cd/m² was presented for 3 min (LU) or 10 min (UIC), and light-adapted luminance–response functions were obtained. In separate sessions, additional luminance-response functions were measured with chromatic test flashes produced by Wratten filters (nos. 98, 61, 44, 29, and 16), which confirmed that the dark-adapted ERG responses of our patient were rod derived and his light-adapted responses were cone derived.

In addition, ERGs were recorded to flashes of extended duration presented against a rod-desensitizing adapting field. The stimuli were presented in a two-channel optical system, with one channel providing a steady Ganzfeld adapting field, while the other delivered the stimulus flash. A pair of Kodak Ektagraphic projectors served as light sources for the two channels, with additional lenses providing collimated beams that transilluminated a hemisected Ping-Pong ball. The duration of the rectangular stimulus flash was controlled by a Uniblitz electronic shutter (Vincent, Rochester, NY). The stimulus luminances were controlled with neutral density filters (Optics for Research, Caldwell, NJ). The pupil of the test eye was dilated as described, and after insertion of the contact-lens electrode, the eye was adapted for 10 min to a Ganzfeld background of 2.1 log cd/m². Stimulus flashes (constant luminance of 3.7 log cd/m²) were presented in order of increasing duration against the adapting field. At each duration, responses to five flashes, with a 1-sec interflash interval, were averaged. The stimulus and adapting field luminances were calibrated with a Spectra Spotmeter (Kollmorgen, Newburgh, NY).

We compared the ERG findings of our patient with those of representative visually normal subjects and two patients with CSNB of the complete type. The characteristics of the first patient with CSNB were described in a previous report (subject 1 in that study). The second patient with CSNB was a 16-yr-old boy with a visual acuity of 20/30 and a refractive error of \(-7.00 + 0.25 \times 100\°\) in the tested eye. His fundus showed a prominent choroidal pattern and other changes consistent with high myopia. Informed consent was obtained from all subjects after the nature of the procedure had been explained fully.

**Results**

The dark-adapted rod ERG responses of our patient with melanoma were similar in waveform both before and after chemotherapy (Fig. 1, middle two tracings). Both responses showed a selective reduction in b-wave amplitude and an absence of oscillatory potentials (OPs) compared with the normal response (Fig. 1, top tracing). Consequently, these ERG abnormalities were present before vincristine therapy. (The overall amplitude difference between the two waveforms of this patient may be caused by a difference in reference electrode positions.) In addition, the responses from this patient were similar in waveform to the ERG of the second patient with CSNB (Fig. 1, bottom tracing).

![Fig. 1. Dark-adapted ERG responses to a strobe flash for (from top to bottom): a representative normal subject (UIC), with a- and b-waves indicated; right eye of the melanoma patient before chemotherapy (LU); right eye of the melanoma patient after chemotherapy (UIC); and CSNB patient 2 (UIC). Flash luminances were 0.9 (LU) and 0.8 (UIC) log cd × sec/m². In this and the following figures, 0 on the abscissa indicates time of flash onset.](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933165/ on 06/24/2017)
The response properties of the waveform recorded from our patient with melanoma at UIC (Fig. 1, third tracing) were compared with those of a group of 96 normal control subjects. Both the a-wave amplitude (585.9 μV) and a-wave implicit time (14.4 msec) of our patient's rod system ERG were normal (normal ranges, 342–606 μV and 12.0–15.2 msec, respectively), as they were in three subsequent testing sessions over the course of the next 7 months. By contrast, the amplitude of the rod system b-wave (429.7 μV) was below normal (normal range, 527–1040 μV), and the b-wave implicit time (31.6 msec) was slightly shorter than normal (normal range, 32.6–53.2 msec).

The light-adapted (cone-isolated) ERG responses of our patient with melanoma were similar in waveform both before and after vincristine therapy (Fig. 2, bottom two tracings). Both responses showed a selective reduction in the amplitude of the b-wave and a diminution of the OPs compared with the normal response (Fig. 2, top tracing). We compared the response properties of the waveform recorded at UIC (Fig. 2, bottom tracing) with those of a group of 31 normal control subjects. Both the a-wave amplitude (58.6 μV) and the a-wave implicit time (14.4 msec) of our patient's cone system response were normal (normal ranges, 50.8–121.1 μV and 11.6–15.2 msec, respectively). However, his cone b-wave amplitude (89.8 μV) was below normal (normal range, 148.4–351.6 μV), and his cone b-wave implicit time (39.6 msec) was slightly longer than normal (normal range, 28.4–35.6 msec).

The abnormal cone system ERGs in this patient were similar to those of patients with CSNB. For example, the cone-isolated responses of our patient (Fig. 3, left column) were comparable to those of the second patient with CSNB (Fig. 3, middle column) over the range of flash luminances used, and the responses of both patients were unlike the normal response (Fig. 3, right column). The difference from normal was most pronounced at the highest flash luminances. Under these conditions, the peaked b-wave and prominent OPs that characterized the normal cone ERG response were reduced markedly in both patients. However, the i-wave, which is a late positive component after the b-wave and is thought to be related to an “off” response, was similar in amplitude and timing in all three subjects.

Previous studies have established that the normal cone b-wave responses (Fig. 3) consist of both “on” and “off” components. These components become more separated at longer flash durations (Fig. 4). The responses in the right column of this figure represent the light-adapted ERG responses of a normal subject to flashes of constant luminance but differing duration (indicated by horizontal calibration bars). At a flash duration of 100 msec, the normal
Fig. 4. ERG responses (UIC) to flashes of a constant luminance (3.7 log cd/m²) but of different durations (indicated by the horizontal calibration bars and denoted in milliseconds at the far right). Responses were obtained against a rod-desensitizing adapting field of 2.1 log cd/m² from the left eye of the melanoma patient (left column), CSNB patient 1 (middle column), and a representative normal subject (right column), with ON and OFF responses indicated.

Fig. 5. ERG responses (UIC) of the melanoma patient (thick tracings) and a representative normal subject (thin tracings), replotted from Figure 4. Responses of the two subjects are positioned vertically such that they coincide at time of flash onset. Flash durations in milliseconds are indicated at the right of each pair of waveforms.

Discussion

Night blindness, a sensation of shimmering lights, and ERG abnormalities were present in our patient with cutaneous malignant melanoma before the administration of vincristine sulfate, and these characteristics did not change appreciably after chemotherapy was administered. Therefore, although vincristine can produce alterations in the ERG of the arterially perfused cat eye that resemble those observed in patients with this type of acquired night
blindness, vincristine chemotherapy is not necessary for the development of this condition. Instead, our findings support the hypothesis that the acquired night blindness and other visual symptoms are a paraneoplastic effect of the malignant melanoma, as suggested previously. Thus, this disorder appears to be one of several paraneoplastic syndromes, in which neurodegenerative disease is a remote effect of the cancer and not related to direct tumor cell invasion.

The paraneoplastic night blindness associated with a malignant melanoma is distinct from cancer-associated retinopathy (CAR), a paraneoplastic retinal disorder characterized by clinical, electrophysiologic, and histopathologic evidence of degeneration and loss of rod and cone photoreceptors. It also differs from the acute Vogt-Koyanagi-Harada-like syndrome that was reported to occur in one patient in association with a metastatic cutaneous melanoma.

In that patient, as in those with CAR, ERG a- and b-waves were reduced markedly in amplitude, indicating widespread photoreceptor cell dysfunction. By contrast, our patient had a-wave amplitudes and implicit times for both rod and cone systems that were normal, a finding that is consistent with normal functioning of the photoreceptor cell outer segments.

Some paraneoplastic syndromes appear to involve an autoimmune response. In particular, recent evidence indicates that the sera from patients with CAR contain autoantibodies that react with antigens derived from photoreceptors and ganglion cells. The serum of our patient with melanoma showed evidence of antibodies reacting against retina (Thirkill CE, Ho Y-K, personal communication) but not against the retinal CAR antigen (Thirkill CE, personal communication). This result further distinguishes this form of paraneoplastic night blindness from the CAR syndrome and suggests a possible involvement of the autoimmune system.

The amplitudes of both rod and cone system b-waves were reduced in our patient with melanoma. Evidence indicates that the normal rod b-wave results from ionic fluxes that are driven predominantly by "on" or depolarizing bipolar cells (DBCs), which appear to be the only type of bipolar cell that subserves the mammalian rod pathway. Consequently, the reduced amplitude and implicit time of the rod b-wave in our patient probably resulted from a defect in neurotransmission between rods and DBCs. According to our findings, the decreased amplitude of the cone system b-wave of this patient resulted from a reduction in the "on" response component; the "off" response was normal. Because the cone "off" response appears to be generated predominantly by cone photoreceptors and hyperpolarizing bipolar cells (HBCs), this finding shows a normal light-induced modulation of cone neurotransmitter and normal HBC function in this patient. A selective reduction in the "on" response component could be explained by a postsynaptic defect in the cone DBCs, which generate this response. Accordingly, a general defect in synaptic transmission between photoreceptors and DBCs could account for both the abnormal rod and the abnormal cone ERG responses found in our patient, as has been suggested previously for patients with CSNB.

There are several functional differences between DBCs and HBCs. For example, they appear to have dissimilar types of glutamate receptors. The DBCs bind the glutamate analogue 2-amino-4-phosphonobutyrate. The HBCs bind cis 2,3-piperidine-dicarboxylic acid and kynurenic acid. In addition, the mechanism of the response to glutamate is distinct. By contrast with the HBCs, glutamate uptake by the DBCs activates a second messenger system involving a G-protein-mediated process. Given these differences between HBCs and DBCs, there may be differential effects of disease on signal transmission between photoreceptors and the two distinct types of bipolar cell.

In conclusion, there are striking similarities between the acquired form of night blindness associated with cutaneous malignant melanoma and CSNB. Both conditions involve a substantial elevation of rod absolute thresholds and selective reductions in the amplitudes of both rod and cone ERG b-waves. In both disorders, cone ERG abnormalities result from a selective reduction in the "on" response component of the cone system ERG. Although there are a few differences between these disorders, such as a rapid onset of night blindness, a sensation of shimmering lights, and foveal color vision abnormalities in acquired night blindness, the functional similarities between the two disorders suggest that they may share a common underlying pathophysiologic mechanism, specifically a defect that is relatively selective for retinal "on" pathways.

Key words: cutaneous melanoma, paraneoplastic, electroretinogram, night blindness, cones

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