Corticosteroid Treatment for Melanoma-Associated Retinopathy
Effect on Visual Acuity and Electrophysiologic Findings

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Background: Visual disturbance in the course of melanoma is rare. Specific localized metastases and drug toxic effects are frequently the cause. Recognition of a retinopathy raises several questions when the diagnosis of melanoma-associated retinopathy (MAR) can be confirmed. Descriptions of such patients in dermatologic literature are rare and deserve attention because therapeutic decisions are mandatory.

Observations: A 70-year-old woman had a first melanoma in 1985 and a second primary melanoma in 1994. Axillary lymph node involvement occurred in November 2000, leading to surgery and chemotherapy. In December 2001, she had sudden bilateral visual loss, with shimmering blobs of color and flickering photopsias. Computed tomography and cerebral magnetic resonance imaging ruled out localized tumor on the eyes or optic nerves or evolution of disease. Ophthalmologic examination revealed a bilateral posterior uveitis, with hyalitis and progressive destruction of retinal pigment. The electrophysiologic data confirmed the diagnosis of MAR. Symptoms improved after systemic corticosteroid therapy, with no relapse after tapering doses despite worsening of melanoma.

Conclusions: As a rare paraneoplastic visual syndrome possibly leading to blindness, MAR is characterized by bipolar cell involvement without photoreceptor cell impairment. Also, MAR is linked to the presence of autoantibodies directed against melanoma antigens that cross-react with the rod bipolar cells of the retina. Corticosteroid therapy is rarely beneficial. Our case of MAR is noteworthy because it involved a woman, was associated with an uveitis, and improved with corticosteroid therapy.

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LOSS OF VISION IN PATIENTS with melanoma may result from a variety of mechanisms, including metastatic invasion of the optic nerves or central visual pathways, meningeal infection by opportunistic organisms, toxic effects from using radiation chemotherapeutic or immunotherapeutic agents, and paraneoplastic conditions.

Melanoma-associated retinopathy (MAR) is a rare visual paraneoplastic syndrome, and only a few cases have been reported so far. Typically, months to years after diagnosis of metastatic cutaneous melanoma, patients experienced the sudden onset of night blindness. They complained of visual loss, with flickering shimmering lights in the central visual field. The electroretinograms resemble those of congenital stationary night blindness, with reduced b-waves and normal dark-adapted a-waves.

Clinical and electrophysiologic data suggest that this retinopathy is the result of antibodies produced against retinal bipolar cells or retinal cellular components. The prognostic significance of this syndrome in the course of melanoma is not well established because the autoimmune response may or may not prevent further dissemination of the disease. We report a case of a patient with MAR and unusual associated severe uveitis who had a good response to corticosteroid treatment, which improved not only the clinical aspect but also the electrophysiologic data. Other causes of visual loss in melanomas are discussed.

CASE REPORT

A 70-year-old white woman had undergone surgery for a malignant melanoma of the right arm in 1985 (Breslow tumor thickness, 0.4 mm) and a second malignant melanoma of the back in 1994 (Breslow tumor thickness, 1.2 mm), with no known familial history. During November 2000, regional lymph node involvement and distant skin metastasis were noted (AJCC stage IV).

The patient had completed surgery of the lesions and received 6 courses of dacarbazine. Clinical and radiologic examinations
revealed no further evidence of recurrence of metastasis until December 2001. At that time, the patient complained of acute painless bilateral loss of vision. She noted “shimmering blobs of yellow and gold,” intermittent flickering photopsias, and “moving lights.” The patient did not indicate night blindness. She had no history of night blindness or other visual loss, and there was no family history of night blindness or retinal degeneration. General examination confirmed the absence of hypertension and diabetes mellitus.

Findings from cerebral and orbital computed tomography were normal. Magnetic resonance imaging showed no abnormalities of the globes, optic nerves, orbits, or brain. General examination and total-body computed tomography revealed no extension of the melanoma.

In January 2002, the oculary findings were as follows: best-corrected visual acuity of 1.2/40 OD and 2/40 OS, no afferent pupillary defects, and no distortion using an Amsler grid. Cranial nerves III to XII and ocular motility were normal.

Slitlamp examination revealed a cicatricial leukoma in the right eye and fewer white keratic precipitates in both eyes. Intraocular pressures were normal. The lens had small cortical opacities. Results of the fundus examination showed bilateral multiple fine white cells in the vitreous and nonspecific changes in the retinal pigment epithelium with mottling pigment in the posterior pole and the middle periphery (Figure 1A). There was no evidence of disk edema, vessel or macula change, or loss of the nerve fiber layer. According to Lanthony test results, color vision was normal. Goldmann kinetic perimetry showed mild constriction of the peripheral isopter associated with an enlarged blind spot (Figure 2A).

Fluorescein angiography showed minor leakage of dye from the left optic disc (Figure 1A). There was no evidence of capillary or perfusion defects, and the macula appeared normal on both sides. The electroretinogram showed a decreased late scotopic b-wave, and a relatively normal photopic early dark-adapted a-wave response as seen in congenital stationary night blindness or in MAR (Figure 3A). Clinical data were in favor of a posterior uveitis, with hyalitis and bilateral progressive destruction of the retinal pigment epithelium, confirmative of the MAR that we suspected. The patient was treated with 1 intravenous bolus of corticosteroids, 750 mg/d for 3 consecutive days, followed by oral corticosteroids, 60 mg/d for 1 month. At that time, the patient noted a clinical improvement, which allowed tapering of oral corticosteroids during a 7-month period without relapse of ophthalmologic symptoms. The follow-up ophthalmologic examination confirmed the complete healing of the uveitis in the right eye (Figure 1B) and the decrease in vitreous cells in the left eye. Visual perimetry (Figure 2B) and electrophysiologic (Figure 3B) findings were notably improved. The clinical pattern and the evolution were in favor of MAR. In September 2002, the patient was diagnosed as having iron deficiency anemia and melena. The endoscopic examination showed multiple gastric and duodenal metastases. She died on November 5, 2002, without any relapse of ocular symptom.

Visual disturbances in patients with metastatic malignant melanoma may result from a variety of mechanisms, including metastatic invasion of the brain, optic nerves, or intraocular tissue. These causes can be excluded by clinical and radiologic examination findings. Toxic effects from chemotherapeutic agents such as vincristine have already been described. Recently, interferon α therapy has been associated with ocular adverse effects, including dryness and retinopathy. Their occurrence is correlated with high concentrations of inter-

Figure 1. A, Pretreatment angiogram shows changes in the retinal epithelium with mottling pigment (white arrow), global opacity of the vitreous due to multiple white cells (arrowhead), and pale optic disc (black arrow). B, Posttreatment angiogram shows improvement. Retinal vessels are now visible (arrow).

Figure 2. A, Goldmann perimetry before treatment shows constriction of the peripheral isopter (arrows) and an enlarged blind spot (arrowhead). B, Goldmann perimetry after treatment shows improvement.
Vascular endothelial cells are directly affected by interferon α, and the retinopathy associated with interferon is linked to the disturbance of retinal capillary perfusion. Fundus examination showed cotton wool exudates and retinal hemorrhages. In most cases, symptom improvement was evident after cessation of therapy.

Figure 3. A, Pretreatment electroretinogram shows an abnormal scotopic b-wave response. B, Posttreatment electroretinogram shows more than 30% of b-wave amplitude increases at late scotopia.
Less frequently, visual loss may be caused by an autoimmune disorder characterized by a high titer of serum antibodies directed against antigens shared by the tumor cells and neurons in the retina or optic nerve, as seen in MAR.

Melanoma-associated retinopathy is a visual parasellar syndrome that is a rare occurrence in some patients with cutaneous malignant melanoma. It has to be separated from carcinoma-associated retinopathy, which is more frequent and better understood. In carcinoma-associated retinopathy, ocular symptoms generally precede the diagnosis of cancer (most commonly small cell carcinoma of the lung). The patient has first ring scotoma in the visual field and progressive visual loss. Retinal histopathologic analysis shows degeneration of rod and cone cells caused by cytotoxic autoantibodies against a retinal protein, recoverin. Electroretinography shows alteration of scotopic and photopic amplitudes, and immunosuppressive treatment seems to be effective.

Melanoma-associated retinopathy is rarely reported in the dermatologic literature. However, Pfoehler et al recently argued for the higher-than-expected prevalence of subclinical MAR symptoms when active ophthalmologic detection is performed. The salient finding of our study is the complete clinical response of uveitis confirmed by improvement of electrophysiologic data. This improvement in visual acuity has never been shown before, to our knowledge. Visual disturbance in MAR is believed to result from a defect in transmission of signals from the photoreceptors to the inner retina secondary to auto-antibodies against a melanoma antigen cross-reacting with the rod bipolar cells. In MAR, patients frequently have an established diagnosis of cutaneous melanoma, usually associated with nonocular metastasis (often lymph node metastasis). It affects predominantly males, unlike our case, with a male-female ratio of 4.7:1. The patient characteristically has an acute onset of decreased vision, a sensation of shimmering lights, and difficulty with night vision. Review of the literature shows only a few observations with deteriorated visual acuity, retinal pigment epithelial changes, the presence of vitreous cells, and pale optic disk, similar to our case.11,13,14 However, the same fluorescein angiographic findings have been described previously.13,18 A pathologic perimetry consisting of concentric restriction of visual fields is more common.9,11

Electroretinography reveals a characteristic pattern of a markedly reduced b-wave, indicating compromised bipolar cell function, and a normal dark-adapted a-wave, indicating normal photoreceptor cell function. Similar findings are seen in congenital stationary night blindness.2 The serum samples from the patient with MAR had elevated levels of IgG reactive with the rod bipolar cells in human retinas according to Milam and Weinstein and coworkers.

Only a few articles mention therapeutic strategy. The use of immunosuppressive agents (eg, corticosteroids), plasmapheresis, or intravenous immunoglobulins has been largely ineffective. Only plasmapheresis reduced antibody titers, but it did not improve ocular symptoms. Our case is noteworthy because the MAR improved with corticosteroid treatment.

This improvement of ocular symptoms was confirmed by the results of fundus examination and electro-ophysiologic studies, which gave a clue in favor of the cure of MAR for this patient. Many cases with prolonged survival delay have been reported. Some discuss the interest in treatment with immunosuppressive agents. In our case, the immunosuppression related to corticosteroid therapy may have played a role in the development of subsequent metastasis. However, according to Keltner et al, the survival delay in patients with MAR is not modified by the treatment. In our opinion, the prognostic value of MAR in the course of melanoma is still debatable.9,10,13,14

In our opinion, MAR must be considered as a possible cause of visual symptoms in patients with a known history of cutaneous melanoma. Furthermore, inquiry regarding visual symptoms should be included in the clinical evaluation of patients with melanoma.

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