The Absent-Minded Professor: An Unusual Complication of Melanoma

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By Ragini Kudchadkar, MD [1], Rene Gonzalez, MD [2], William Robinson, MD, PhD [3], Maude Becker, RN [4], Krista Treichel, RN [5], Alan Kimura, MD [6], and Karl Lewis, MD [7]

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E. David Crawford, MD
Al Barqawi, MD

Guest Editors
University of Colorado Health Sciences Center
and University of Colorado Cancer Center
Denver, Colorado

The patient is a geology professor who was evaluated in our multidisciplinary cutaneous oncology clinic for a new diagnosis of malignant melanoma with subsequent development of metastatic disease and melanoma-associated retinopathy.

History

The patient initially presented to our clinic in 1998. At that time, he was a 57-year-old geologist with a history of extensive sun exposure who had a pigmented lesion biopsied from his right posterior auricular region. The pathology revealed a Clark’s level IV, 1.28-mm malignant melanoma. He subsequently underwent wide local excision with concurrent sentinel lymph node biopsy. The reexision specimen revealed no residual melanoma, and three lymph nodes were removed, none of which showed any evidence of metastatic melanoma. After much discussion with the patient, he elected to enroll on an adjuvant clinical trial of interferon with or without tamoxifen. He was randomized to receive interferon alone. He received interferon at 3 million units subcutaneously three times a week for a total of 18 months. The patient tolerated this treatment well, with only fatigue as a complaint. He was then followed with close observation.

He did very well until May of 2002, when he began to complain of trouble with his vision. He reported yellow and white flashing lights and floaters. An optometrist initially evaluated him but found no etiology for these symptoms. Magnetic resonance imaging (MRI) of the brain was performed in June 2002 to further evaluate these symptoms. The scans showed no evidence of metastatic melanoma. Despite this initial negative workup, the patient continued to report worsening vision with persistent flashing lights as well as new symptoms of memory loss. He was therefore evaluated by ophthalmology. Because of his symptoms, there was concern about lymphoma as a possible cause, and therefore a vitreous biopsy was performed. The biopsy was interpreted as vitritis. The pathology
revealed inflammatory white cells, no definitive pigment cells, and no lymphoma, and all cultures were negative.

Symptoms particularly worsened in September 2002, with progressive short-term memory loss and difficulty with verbal expression. The patient stated, “I am losing my mind.” A repeat MRI of the brain was performed, revealing a 5×4.4×4 cm left frontal hemorrhagic metastasis. He was admitted to neurosurgery and began therapy with steroids and antiepileptics. A left craniotomy with complete resection was performed, and the pathology was consistent with metastatic melanoma. Further evaluation with imaging demonstrated mediastinal lymphadenopathy and only postoperative changes on brain MRI. In October 2002 the patient was enrolled on a clinical trial with EPO906A, an experimental epothilone. FIGURE 1

The patient’s short-term memory improved after treatment of the intracranial metastasis, but his visual complaints of flashing lights and floaters persisted. There was no improvement with systemic steroids. In December 2002, a retinal specialist evaluated him. At that time, the patient reported a bright yellow-white light that moved in and out of visual fields and faded within seconds. (Figure 1). Moth-eaten visual fields and an essential normal retinal exam were documented (Figures 2 through 4). Visual acuity was intact with 20/30 OD (oculus dexter, or right eye) and 20/40 OS (oculus sinister, or left eye). An electroretinogram revealed a marked loss of b-wave amplitude, pathognomonic for melanoma-associated retinopathy (Figure 5). FIGURE 2

FIGURE 1

Patient's Own Drawing of His Visual Symptoms

FIGURE 2

Right Eye Visual Field

FIGURE 3

Left Eye Visual Field

FIGURE 4
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fundoscopic Exam

The patient was initiated on intravenous immunoglobulin (IVIg) monthly with stabilization and eventual improvement/resolution of his visual symptoms. He tolerated EPO906A very well and had a complete response to treatment with resolution of the mediastinal lymphadenopathy. The drug was eventually discontinued after 12 months of treatment. The IVIg is still required monthly. We have been unable to discontinue the IVIg, as his vision deteriorates with attempts to taper the dose or increase the treatment interval. He is currently still being followed by the multidisiplinary team and shows no evidence of melanoma.

Discussion

Ophthalmology Review

Dr. Ragini Kudchadkar: Dr. Kimura, can you please review for us the ocular findings of melanoma-associated retinopathy (MAR)?

Dr. Alan Kimura: Patients with MAR often provide a history of photopsias and shimmering patches of color, and in this case shimmering yellow lights, the reappearance of which is a marker for too long an interval between IVIg treatments. Visual acuity is typically fairly well preserved. The largest review of patients with MAR documented a visual acuity of better then 20/60 in greater than 80% of patients.[1] Visual fields, however, are typically affected. Our patient showed constriction in visual fields with central scotomas. Though this type of presentation is common, there are many reports of patients with MAR that have normal visual fields. Thus, there are no specific visual field findings in MAR.

Funduscopic exam is generally normal in these patients. The largest series of patients in the literature demonstrates that approximately half have an essentially normal funduscopic exam.[1] In our patient, funduscopic exam was essentially within normal limits; however, occasional window defects were noted. These are not of clear significance. Other funduscopic findings that have been documented in the literature are optic nerve pallor, vessel attenuation, retinal pigment epithelium changes, and vitreous cells, although these finding are more characteristic of cancer-associated retinopathy (CAR), a paraneoplastic disease with autoantibodies directed against recoverin, a critical moiety of the visual cycle found in the photoreceptor.

Vitreous fluid analysis is only documented in a few patients with MAR. Among those patients (n = 10), most do show some cells with varying degrees of inflammation.[1] Melanoma cells are rarely seen, with only four documented cases throughout the literature. FIGURE 5

Electroretinogram

The most important clinical diagnostic test is the electroretinogram (ERG). ERG is a measure of the electrical response of the retina to varying stimuli of light, under dark-adapted, then light-adapted states. The a-wave represents photoreceptor function, and the b-wave represents inner retinal function, reflecting either Müller cell or bipolar cell function. The classic finding of MAR, as demonstrated by our patient (Figure 5), is the so-called “negative ERG” featuring a low b/a-wave ratio in the “maximal, combined rod and cone response.” This is seen with a markedly reduced b-wave and a normal dark-adapted a-wave, which in the right clinical scenario is pathognomonic for MAR. The loss of the b-wave is due to an autoimmune response involving antigens located within the bipolar layer. Selective b-wave loss on ERG is also seen in congenital stationary night blindness, and
a number of other inherited and noninherited toxic states (Table 1).

**Pathophysiology**

Dr. Kudchadkar: Dr. Gonzalez, can you discuss how the phenomenon of MAR develops?

Dr. Rene Gonzalez: MAR is essentially an autoimmune disease. Autoimmune disease involves molecular mimicry in which tumor antigens share similar epitopes to patient self-epitopes leading to a cross-reaction. Activated T and B cells respond to the foreign antigen, but they also react to the self-proteins because they share similar peptide sequences. This is what leads to the damage of self-tissue.[2] Although this general concept is likely true, there are many hypotheses as to the exact pathophysiology of MAR. Cancer-associated retinopathy may sometimes be related to the p53 gene mutation that is documented in many cancer cells. Mutated p53 produces the recoverin protein that is highly immunogenic and thus leads to antirecoverin antibody production.[3,4] TABLE 1

<table>
<thead>
<tr>
<th>Differential Diagnosis of Loss of B-wave on ERG</th>
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<tr>
<td>X-linked juvenile retinosis</td>
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<tr>
<td>Congenital stationary nightblindness</td>
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<tr>
<td>Oguchi’s disease</td>
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<tr>
<td>Myotonic dystrophy</td>
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<tr>
<td>Batten’s disease (neuronal ceroid lipofuscinosis)</td>
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<tr>
<td>Autosomal dominant neovascular inflammatory vitreoretinopathy</td>
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<td>Quinine toxicity</td>
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<tr>
<td>Methanol toxicity</td>
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<tr>
<td>Siderosis</td>
</tr>
<tr>
<td>Acute-central retinal artery occlusion</td>
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<tr>
<td>Acute-central retinal vein occlusion</td>
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<td>Melanoma-associated retinopathy</td>
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This IgG antibody can penetrate the blood-retina barrier and bind to recoverin in the photoreceptor cells. This leads to increased phosphorylation of the molecule rhodopsin, which is involved in the phototransduction pathway, thus causing activation of the caspase-dependent apoptotic pathways and leading to photoreceptor cell death.[4]

Western blots have been used to analyze patients’ serum against normal donor retinal proteins.[5] They essentially show antiretinal IgG bands of activity. The antibodies are active against a number of proteins, not just recoverin. The antibodies have also been found against alpha-enolase, arrestin, carbonic anhydrase, TULP-1, photoreceptor cell–specific nuclear proteins, and heat shock protein 70.[5] The exact mechanism of photoreceptor death from these other antibodies is not clearly understood.

Some cases of MAR have no detectable antibodies by Western blot. However, many of these reports have been shown to have positive bipolar staining on normal human histologic slides and counterstaining for human immunoglobulin.[1,6,7] These findings have not been documented in all patients with no detectable antibodies by Western blot.

Histologically one can see a marked reduction in the density of bipolar cells and secondary trans-synaptic atrophy of ganglion cells.[8] This correlates well with the ERG findings and pathophysiology in MAR patients that were discussed earlier.

Overall, MAR is secondary to an antibody triggering death of bipolar cells. These antibodies can be variable, but treatment should be aimed at suppressing antibody production, removing the antibody from circulation, and/or blocking antibody action.

**Melanoma and MAR**

Dr. Kudchadkar: Dr. Lewis, does MAR develop in patients with a specific stage of melanoma?

Dr. Karl Lewis: There is no direct correlation between melanoma stage and the development of autoimmune retinopathy. However, in the largest series of patients reported, 28 of 62 had metastatic disease.[1]
This suggests that more patients with advanced disease develop MAR. Given that it is thought that the antibodies develop secondarily to a cross-reaction between melanoma and self, one could theorize that the greater the amount of disease, the more likely one is to develop antibodies. However, this is yet to be proven.

Dr. Kudchadkar: Dr. Lewis, is the development of MAR related to prognosis?

Dr. Lewis: Given the rarity of MAR, it is very difficult to prove a relationship between the syndrome and prognosis. However, many have hypothesized that patients who develop autoimmune disease have a better prognosis compared to those who do not. This hypothesis is prevalent throughout many different cancer types, not just melanoma.

Authors of case reports involving spontaneous tumor regression have theorized that the patient’s immune system produced antibodies to destroy the cancer cells.[9-11] In lung cancer, antineural and antinuclear antibodies have been shown to be positive stage-independent prognostic factors.[12] This has been seen in gynecologic cancer patients as well, with autoantibodies to heat shock protein associated with improved survival.[13]

Approved therapies for melanoma include immune therapies such as interleukin-2 (Proleukin) and interferon. The fact that melanoma responds to immune therapy is further evidence that autoimmunity may be a favorable prognostic factor. Gogas et al evaluated melanoma patients treated with interferon alfa-2b (Intron A) and found that the appearance of autoantibodies or clinical manifestations of autoimmunity were associated with a statistically significant improvement in survival.[14] Overall, though, there is not enough evidence to prove MAR as a favorable prognostic factor in melanoma patients.

Dr. Gonzalez: If autoimmunity is hypothesized to be a good prognostic indicator, is there any indication that treatment of the retinopathy will decrease survival?

Dr. Lewis: Given the rarity of the disease, this is another question for which it is difficult to have a conclusive answer. If our patient has a clinical indication, the answer to your question is that the treatment of the retinopathy does not alter prognosis. Theoretically, immunosuppression in melanoma would be harmful because of the role of immunity in this disease. There is no conclusive evidence that this is true in the treatment of MAR. However, if the visual symptoms are minimal and nonprogressive, one may want to avoid immunosuppression in light of the theoretical risks.

Dr. Kudchadkar: In the mid-1970s, Hoyt first documented paraneoplastic-associated blindness as a remote complication of cancer.[15] Besides melanoma, other cancers associated with cases of retinopathy are those of the lung, ovaries, and colon. Though the presence of this phenomenon in cancer patients is rare, the diagnosis of autoimmune retinopathy should trigger a cancer workup in individual patients. Colonoscopy and chest-x-ray are indicated in patients diagnosed with autoimmune retinopathy but no prior history of cancer, especially in smokers or those greater than 50 years of age.

Treatment

Dr. Lewis: What are the treatment options for MAR?

Dr. Gonzalez: Treatment should be aimed at either blocking antibody function or decreasing antibody production. Most commonly, steroids are used initially, but alternatives like IVIg and plasmapheresis have also been used. There is no standard of care in the treatment of MAR. Although steroids are commonly tried initially, most case reports do not document success with this treatment.[16] Six of seven patients in one case-series failed to respond to steroids alone.[1] Steroid doses are commonly about 1 mg/kg, with most case reports documenting the use of 60 to 80 mg of prednisone daily. One case report demonstrated an improvement with prednisone, but in this case steroids were combined with azathioprine, gabapentin, and plasmapheresis. IVIg was used in our patient with great clinical success. However, now that we are years from his last documented evidence of disease, the patient still requires a monthly IVIg infusion. The reduction or even elimination of melanoma does not preclude progression of MAR, and this has been documented in other case reports as well.[17] If the infusion of IVIg is delayed, the patient’s visual symptoms return.

Plasmapheresis has been used on rare occasion for the treatment of MAR. However, one must also continue to suppress antibody production with another method, because pheresis will not stop production. There is no definitive treatment for MAR, although steroids, IVIg, and plasmapheresis are the most common treatments documented in the literature. In theory, an anti-B-cell monoclonal antibody like rituximab (Rituxan) might be used; however, there are no reports of its use in MAR or any
cancer-associated retinopathy.

Conclusions

Dr. Kudchadkar: Melanoma-associated retinopathy is a rare but distinct clinical entity that must be considered in any melanoma patient with visual symptoms, especially a flashing lights phenomenon. Visual fields are often affected and ERG can be diagnostic for this disease. If recurrent disease is not documented at the time of MAR diagnosis, one should consider repeat imaging in order to look for recurrent melanoma. The relationship of MAR to melanoma disease status and prognosis remains unclear. Treatment options include prednisone, plasmapheresis, and IVIg. Prednisone and plasmapheresis has had minimal success alone; however, case-reports of IVIg therapy, including this one, have shown some success.

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