

# Melanoma-Associated Retinopathy: A Harbinger of Recurrence for Cutaneous Melanoma

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## Abstract

**Purpose:** To describe a patient with the syndrome of melanoma-associated retinopathy. **Methods:** A 65-year-old woman who had been disease free for more than 10 years after excision of a pretibial cutaneous melanoma presented in May 2001 with loss of vision and flickering lights. Visual field testing, electroretinography, and a comprehensive ophthalmologic examination were performed. Melanoma-associated retinopathy was suspected. The patient's serum was subjected to an immunohistochemical reaction with bipolar retinal cells in culture. A staging work-up was initiated. **Results:** The visual acuity was compromised in both eyes, and the visual fields were constricted, particularly in the left eye. The electroretinogram showed decreased b-wave amplitudes. The patient's serum showed positive immunoreactivity against the retinal bipolar cells, supporting the diagnosis of melanoma-associated retinopathy. Computed tomography of the abdomen revealed a large porta hepatis mass, which was biopsied with fine-needle aspiration and proved to be melanoma. The patient was treated with a short course of oral prednisone (40 mg/day for 1 week followed by 20 mg/day for 2 weeks), and her visual dysfunction resolved. **Conclusion:** Melanoma-associated retinopathy may occur many years after the initial diagnosis of cutaneous melanoma. Visual loss associated with central scotomata and decreased b-wave amplitudes on electroretinography in a patient with a history of cutaneous melanoma should prompt a thorough staging work-up in search of metastatic disease.

## INTRODUCTION

Melanoma-associated retinopathy (MAR) is a form of retinal degeneration that is a paraneoplastic phenomenon occurring in association with metastatic melanoma.<sup>1</sup> It has been postulated that MAR is due to a reaction between the retinal bipolar cells and circulating melanoma-associated autoantibodies.<sup>2</sup> MAR is characterized by the rather sudden onset of visual loss together with night blindness and perception of shimmering or flickering lights and spots. Other features of this syndrome are characteristic congenital stationary night blindness-like pattern on electroretinography, including reduced b-wave amplitudes; central scotomata; and the presence of circulating antibodies as demonstrated via an immunohistochemical reaction to retinal bipolar cells.<sup>1,2,3,4,5,6,7,8,9,10,11,12,13</sup>

MAR is a rare diagnosis. Nineteen cases of MAR have previously been reported in the literature.<sup>1-13</sup> Herein, we report a case of MAR in a patient in whom a recurrence of melanoma was discovered more than ten years after the initial diagnosis because of the ophthalmologic diagnosis of

MAR.

## CASE REPORT

A 65-year-old woman with a history of cutaneous malignant melanoma was referred to the Ophthalmology Clinic at The University of Texas M. D. Anderson Cancer Center in May 2001 because of a sudden onset of bilateral scotomata and blurred vision.

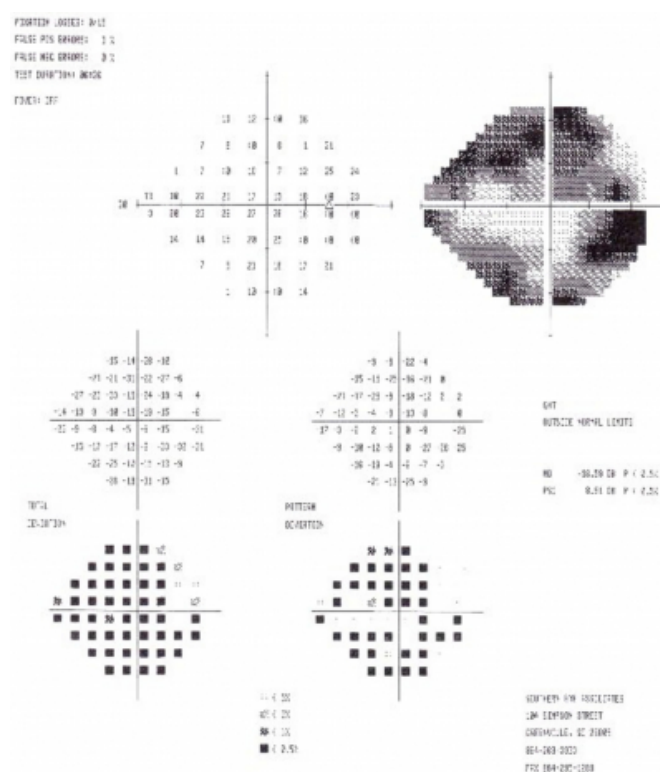
The patient had a history of a melanoma of the right pretibial skin with Breslow thickness of 1 mm, Clark's level III, which was diagnosed and excised in 1984. In 1986, clinically positive lymph nodes were detected in the patient's right groin, and she underwent lymph node dissection followed by adjuvant therapy consisting of combined biochemotherapy. The patient was examined by an oncologist annually between 1986 and 1996 and was considered free of disease during this period. In 1996, the patient was advised that she no longer needed to be monitored for recurrence of her melanoma, and she stopped visiting her oncologist.

In April 2001, the patient developed visual symptoms that included floaters and a sensation of “water splashing in front of her left eye”, which prompted her to see an ophthalmologist. She also experienced difficulty with her central vision and sensed that her peripheral vision was constricted. She was evaluated by her local ophthalmologist, who found her visual acuity to be 20/30 in the right eye and 20/40 in the left eye. The patient underwent formal visual field testing, which revealed a dense central visual field deficit in the right eye (Figure 1A) and a moderately severe visual field defect in the left eye, particularly inferiorly (Figure 1B). Findings on the rest of the ocular examination were essentially normal except for mild depigmentation of the inferior retina in the left eye. MAR was suspected. The diagnosis of MAR was confirmed by a positive immunohistochemical reaction between the patient's serum and the bipolar retinal cells in

culture; this test was performed at a laboratory at the University of California, Davis, using previously described methods.<sup>2,11,13</sup> The patient was treated with oral prednisone 40 mg a day for 1 week and then 20 mg a day for 2 weeks. The prednisone treatment resulted in remarkable improvement of the visual acuity and visual fields. In May 2001, the patient was referred to the Ophthalmology Clinic at M. D. Anderson Cancer Center for further evaluation and treatment.

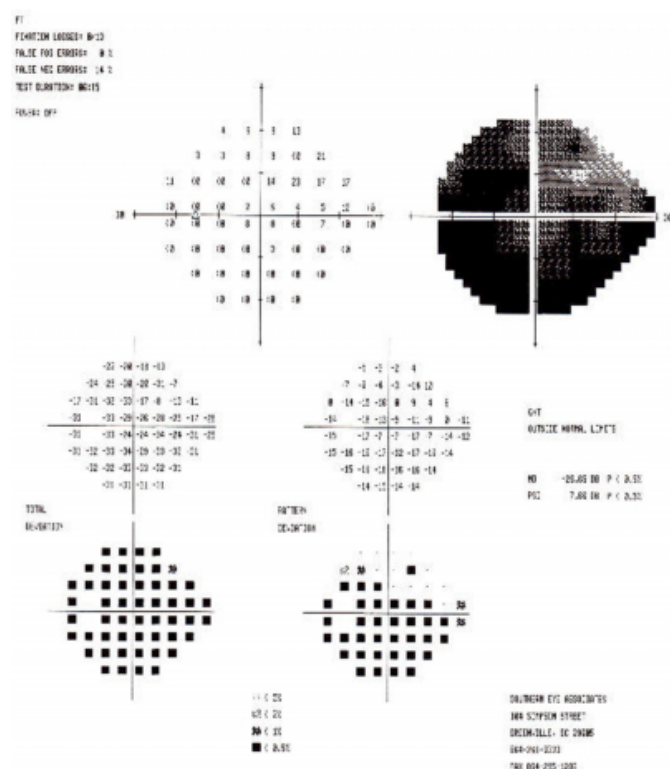
**Figure 1**

Figure 1. Results of Humphrey visual field analysis in April 2001. A) In the right eye, there was a severe central visual field defect.



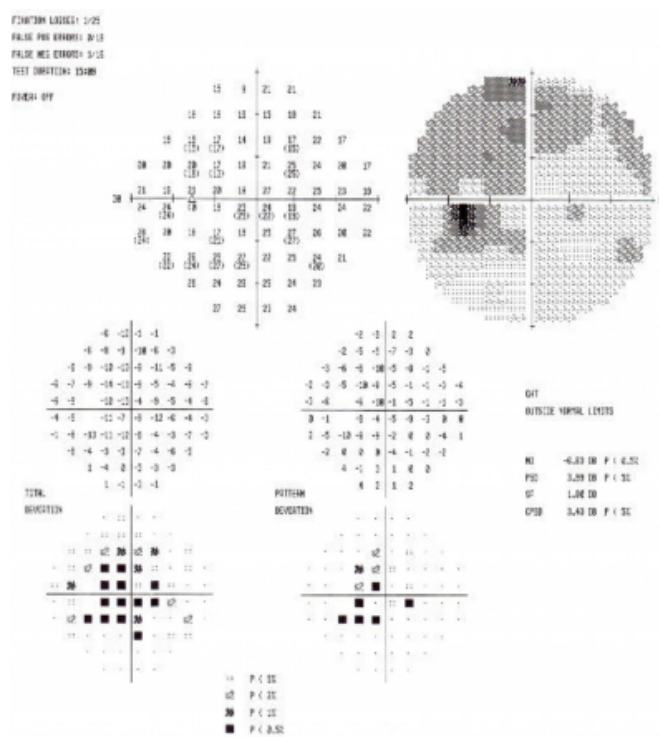
**Figure 2**

Figure 1: B) In the left eye, there was a moderate central and inferior defect.



**Figure 3**

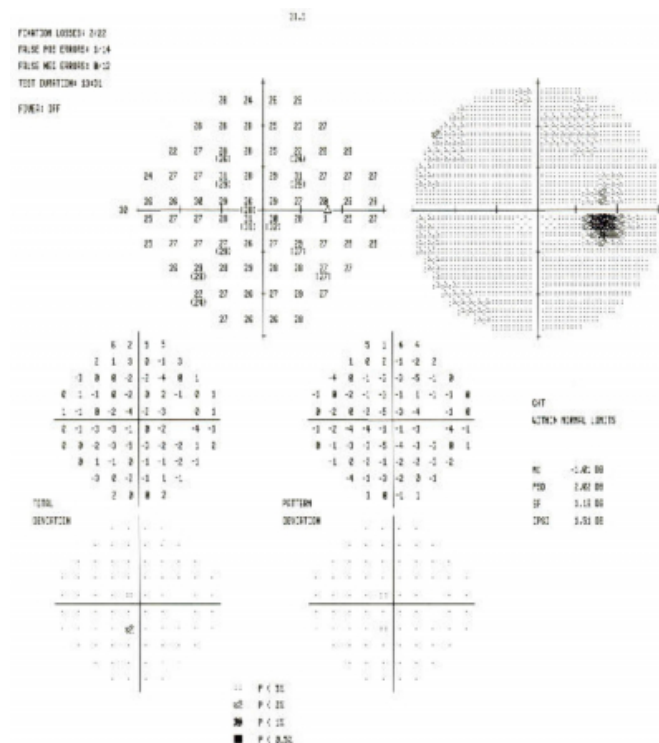
Figure 2. Results of visual field analysis repeated in May 2001 after a short course of oral prednisone showed marked improvement in the right eye (A) as well as the left eye (B).



Findings on the ophthalmologic examination at M. D. Anderson were the same as those on the initial examination in April 2001 except that the visual acuity had improved to 20/20 in the right eye and 20/25 in the left eye and the visual fields had improved as well (Figure 2 A,B). Findings on electroretinography were significant for reduced b-wave amplitudes and reversed a/b ratio; these findings were observed in both eyes but were more significant in the left eye (Figure 3). A systemic work-up was undertaken, including magnetic resonance imaging of the brain and computed tomography of the abdomen and pelvis. A large porta hepatis/peripancreatic mass was discovered on computed tomography of the abdomen (Figure 4). This mass was biopsied with fine-needle aspiration and confirmed to be metastatic malignant melanoma. The patient was treated with several cycles of biochemotherapy consisting of cisplatin, vinblastine, dacarbazine, interleukin-2, and alpha-interferon.

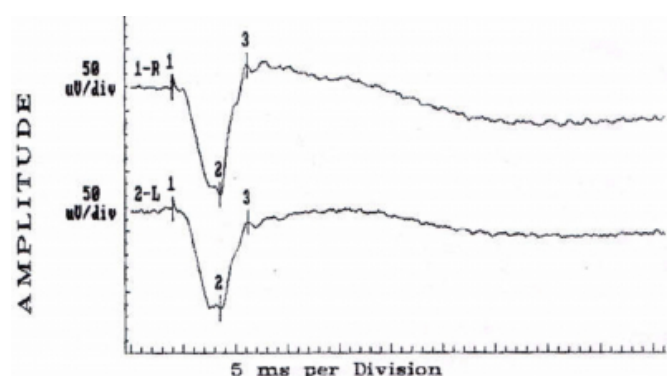
**Figure 4**

Figure 2. Left eye (B).



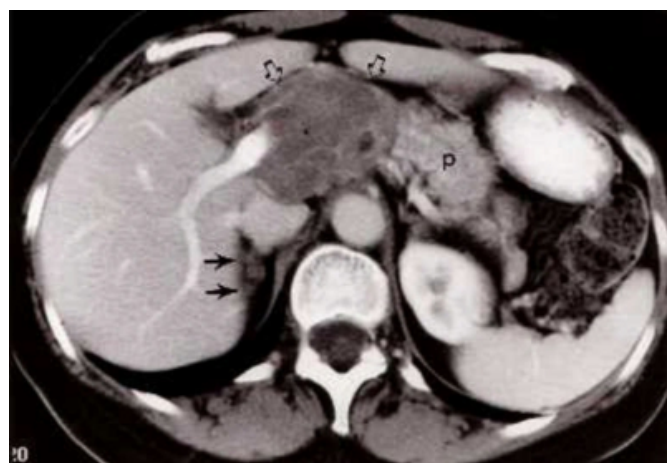
**Figure 5**

Figure 3. Single-flash scotopic electroretinogram revealed a near-normal a-wave (1) but a markedly reduced b-wave amplitude (2).



**Figure 6**

Figure 4. Contrast-enhanced computed tomography at the level of the body of pancreas (p) showing a 6 cm nodal mass (open arrows) displacing the head of the pancreas caudally. Note two nodules arising from the lateral limb of the right adrenal gland (closed arrows), representing either metastasis, or non-functioning adenomata.



## DISCUSSION

Since the original description by Sawyer et al,<sup>14</sup> several cases of paraneoplastic retinopathy, most commonly cancer-associated retinopathy, have been described.<sup>15-16</sup> MAR is a rare form of paraneoplastic syndrome that is distinct from cancer-associated retinopathy. Cancer-associated retinopathy is associated with epithelial cancers (most commonly small cell carcinoma of the lung) and is characterized by gradual onset of night blindness with progressive retinal degeneration that may lead to an extinguished electroretinogram reminiscent of findings in retinitis pigmentosa.<sup>15</sup> In contrast, MAR is associated with a history of cutaneous melanoma, and is associated with decreased b-

wave amplitudes on electroretinography reminiscent of the pattern seen in congenital stationary night blindness.<sup>2,6-8</sup> Whereas cancer-associated retinopathy is associated with immunohistochemical reactivity of affected patients' serum with the inner segments and nuclei of rods and cones and the outer plexiform layer of the retina, in MAR, affected patients' serum reacts with the bipolar cell layer of the retina.<sup>2</sup>

Two mechanisms have been postulated as the pathophysiologic basis for paraneoplastic retinopathy: direct toxic damage to the retina by a circulating product of the tumor cells, or damage by autoantibodies directed against a tumor-specific epitope that cross-react with specific retinal antigens. In the case of cancer-associated retinopathy, a specific retinal antigen, recoverin, is thought to be the retinal component that cross-reacts with the circulating autoantibodies.<sup>17</sup> Although a consistent pattern of immunoreactivity with the bipolar retinal cell layer has been found in most reported cases of MAR, to our knowledge, the specific retinal antigen responsible for immunostaining of rod bipolar cells by sera of patients with MAR has not yet been identified. Also, it is not clear how the putative antibodies against the retinal bipolar cells cross the blood-retinal barrier and cause the observed retinal dysfunction.

Although some investigators have found that immunosuppressive therapy may not be effective in restoring vision in patients with MAR,<sup>2,11,18,19</sup> the visual loss associated with MAR in our patient was remarkably responsive to a short course of oral steroids, perhaps because of early diagnosis. Prolonged use of immunosuppressive therapy may pose a theoretical disadvantage of hampering the immune attack against the melanoma cells.

The characteristic immunohistochemical pattern of reactivity with retinal bipolar cells seen in MAR is not pathognomonic for this syndrome as this pattern of reactivity can also occur in congenital stationary night blindness.<sup>20,21</sup> A history of cutaneous melanoma and onset of visual symptoms late in life suggest MAR as a more likely diagnosis than congenital stationary night blindness.

The case we have reported here demonstrates the importance of recognizing MAR as a harbinger of recurrence of - in most cases - previously diagnosed cutaneous melanoma. MAR may occur after many years of apparent disease-free status. A relatively acute onset of visual loss associated with night blindness, central scotomata on visual field testing, and decreased b-wave amplitudes on electroretinography in a

patient with a history of cutaneous melanoma should prompt a thorough staging work-up in search of recurrent metastatic disease. The patient's serum should be sent for special immunohistochemical testing with cultured retinal cells to confirm the diagnosis of MAR so that appropriate systemic therapy can be instituted as soon as possible.

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## **References**

1. Berson EL, Lessell S. Paraneoplastic night blindness with malignant melanoma. *Am J Ophthalmol* 1988;106:307-311.
2. Milam AH, Saari JC, Jacobson SG, Lubinski WP, Feun LG, Alexander KR. Autoantibodies against retinal bipolar cells in cutaneous melanoma-associated Retinopathy. *Invest Ophthalmol & Vis Sci* 1993;34: 91-100.
3. Alexander KR, Fischmann GA, Peachey NS, et al. 'On' response defect in paraneoplastic night blindness with cutaneous malignant melanoma. *Invest Ophthalmol Vis Sci* 1992;33:477-83.
4. Andreasson S, Ponjavic V, Ehinger B. Full-field electroretinogram in a patient with cutaneous melanoma associated retinopathy. *Acta Ophthalmol* 1993;71:487-90.
5. Rush JA. Paraneoplastic retinopathy in malignant melanoma. *Am J Ophthalmol* 1993;115:390-1.
6. Weinstein JM, Kelman SE, Bresnick GH, et al. Paraneoplastic retinopathy associated with antiretinal bipolar cell antibodies in cutaneous malignant melanoma. *Ophthalmology* 1994;101:1236-1243.
7. Kim RY, Retsas S, Fitzke FW, Arden GB, Bird AC. Cutaneous melanoma-associated retinopathy. *Ophthalmology* 1994;101:1837-1843.
8. Singh A, Milam AH, Shields CL, De Potter P, Shields JA. Melanoma associated retinopathy. *Am J Ophthalmol* 1995;119:369-70.
9. Kellner U, Bornfeld N, Foerster MH. Severe course of cutaneous melanoma associated paraneoplastic retinopathy. *Br J Ophthalmol* 1995;79:746-752.
10. Rougier MB, Hostyn P, Bret-Dibat C, Delauney MM, Riss I, LeRebeller MJ. Paraneoplastic retinopathy associated with cutaneous melanoma. An update apropos of a case. *Jl Fr Ophtalmol* 1995;18:396-403.
11. Boek K, Hofmann S, Klopfer M, Ian U, Schmidt T, Engst R. Melanoma-associated paraneoplastic retinopathy: case report and review of the literature. *Br J Dermatol* 1997;137:457-460.
12. Gittinger JW Jr, Smith TW. Cutaneous melanoma-associated paraneoplastic retinopathy: histologic observation. *Am J Ophthalmol* 1999;127:612-614.
13. Potter MJ, Thirkill CE, Dam OM, Lee AS, Milam AH. Clinical and immunocytochemical findings in a case of melanoma-associated retinopathy. *Ophthalmology* 1999;106:2121-2125.
14. Sawyer RA, Selhorst JB, Zimmerman LE. Blindness caused by photoreceptor degeneration as a remote effect of cancer. *Am J Ophthalmol* 1976;81:606-613.
15. Thirkill CE, Tait RC, Tyler NK, Roth AM, Keltner JL. The cancer-associated retinopathy antigen is a recoverin-like protein. *Invest Ophthalmol Vis Sci* 1992;33:2768-2772.
16. Jacobson DM, Adamus G. Retinal anti-bipolar cell antibodies in a patient with paraneoplastic retinopathy and colon carcinoma. *Am J Ophthalmol* 2001;131:806-808.
17. Adamus G. Antirecoverin antibodies and autoimmune retinopathy. *Arch Ophthalmol* 2000;118:1577-1578.
18. Keltner JL, Thirkill CE, Tyler NK, et al. Management and monitoring of cancer-associated retinopathy. *Arch Ophthalmol* 1992;110:48-53.
19. Guy J, Aptsiauri N. Treatment of paraneoplastic visual loss with intravenous immunoglobulin: Report of 3 cases. *Arch Ophthalmol* 1999;117:471-477.
20. Bech-Hansen NT, Naylor MJ, Maybaum TA, et al. Mutations in NYX, encoding the leucine-rich proteoglycan nyctalopin, cause X-linked complete congenital stationary night blindness. *Nat Genet* 2000;26:319-323.
21. Borkowski LM, Grover S, Fishman GA, et al. Retinal findings in melanoma-associated retinopathy. *Am J Ophthalmol* 2001;132:273-275.

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