Melanoma-Associated Retinopathy

A Paraneoplastic Autoimmune Complication

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Objectives: To study 11 patients with melanoma-associated retinopathy (MAR) to clarify the reliability of various methods of diagnostic testing, to determine the underlying antigenic retinal proteins, and to study the clinical histories and types of associated melanomas.

Methods: Clinical data were obtained from patients with melanoma who developed marked visual problems. Testing included electroretinography, kinetic visual fields, comparative studies of Western blots, and indirect immunohistologic examination to detect antiretinal antibodies, as well as proteomic studies to identify underlying antigenic retinal proteins.

Results: Patients with MAR typically have rapid onset of photopsias, scotomata, and loss of central or paracentral vision. Ophthalmoscopy seldom shows significant changes early, but electroretinograms are abnormal. Results of Western blots and immunohistologic examination can show antiretinal antibodies but not always. Most patients (9 of 11) had a strong family history of autoimmune disorders. Any type of melanoma (cutaneous, choroidal, ciliary body, or choroidal nevi) may be associated with this paraneoplastic autoimmune reactivity. MAR may precede or follow the diagnosis of melanoma. Patients with MAR have the same antigenic retinal proteins that have been associated with cancer-associated retinopathy. In addition, 2 new antigenic retinal proteins, aldolase A and aldolase C, were found.

Conclusions: There was a high prevalence of positive family histories of autoimmune disease in patients with MAR. To confirm the disorder, multiple clinical and serum diagnostic techniques (Western blot or indirect immunohistologic examination) are needed. Two newly observed antigenic retinal proteins, aldolase A and aldolase C, are associated with MAR.


Autoimmune Retinopathy (AIR) was first recognized as a paraneoplastic disorder as early as 1976 in patients with carcinoma, and subsequent studies in the literature showed that AIR could occur with benign and malignant tumors. Melanoma-associated retinopathy (MAR) was initially reported by Gass in an atypical case with vitelliruptivelike yellow retinal lesions, but most MAR cases have diffuse retinal atrophy without pigment deposits. A broader view of 51 cases of MAR was published by Keltern et al summarizing many of the features and some of the controversies. Except for 2 case reports of choroidal melanoma only MAR associated with cutaneous melanomas has been reported.3

Paraneoplastic development of antiretinal antibodies with resulting retinal disease is an intriguing pathologic process and remains poorly understood. There have been reports of retinopathies associated with carcinomas, melanomas, tetratomas, and even lymphomas. Most cases of AIR occur in patients without a history of tumors, but occasionally a history of head trauma or preceding intraocular inflammatory disease may be found. Investigations of cancer-associated retinopathy (CAR) have found that the tumors in these patients aberrantly express proteins normally exclusive to retinal tissue, leading to the production of antibodies directed against these retinal antigens. There are no reports in which primary melanomas have been examined to investigate the presence of retinal proteins, although melanoma cell cultures have demonstrated their presence. The antiretinal antibodies in patients with MAR are associated with progressive panretinal degeneration that frequently results in legal blindness. Patients' early symptoms typically manifest as sparkles and shimmers (photopsias) and blind spots in their vision. On clinical examination, early stages of retinopathy may
be difficult to see clinically, but an electroretinogram (ERG) (a standardized evoked response that measures photoreceptor and inner retinal responses) will clearly show retinal dysfunction and aids in diagnosis of this condition with otherwise minimal retinal changes. Conventional confirmatory evidence for MAR has included examination of serum for antiretinal antibodies by Western blot or measurement of antibody staining of donor retina, particularly bipolar cells, by indirect immunohistologic studies. However, there has been controversy about the best diagnostic tests, with data suggesting that Western blots may be unreliable for detecting antiretinal antibodies in patients with MAR. Milam et al recommended indirect immunohistologic investigations for retinal inner nuclear layer bipolar cell staining as a reliable technique for confirming MAR. To date, no studies have been performed in patients with MAR comparing Western blot with indirect immunohistologic detection of antiretinal antibodies. In addition, the specific antibodies (and their antigenic retinal proteins) involved in MAR have not been systematically examined. We investigated 11 patients with MAR who were initially seen with visual loss and photopsias and who underwent clinical examinations, electrophysiological and psychophysical testing, Western blots, indirect immunohistologic investigations, and proteomic analysis to identify the antigenic retinal proteins. Careful family histories were taken for autoimmune disorders to clarify the genetic autoimmune backgrounds of patients with MAR.

**METHODS**

**CLINICAL EXAMINATIONS**

Eleven patients with histories of melanoma and subsequent retinopathies of unknown origins and 8 patients with CAR and AIR (included for comparison) were examined at the retinal dystrophy clinic at the Kellogg Eye Center, University of Michigan, Ann Arbor. The patients were evaluated using standardized kinetic visual fields, electroretinographic testing, fundus photography, and clinical examinations. Serum samples were obtained after informed consent and were stored at −80°C until studied. As control subjects, 9 healthy volunteers with normal ERGs and no family history of autoimmune diseases were recruited. Informed consent was obtained from all patients and control subjects. The experimental protocol was approved by the University of Michigan institutional review board.

**2-DIMENSIONAL ELECTROPHORESIS**

**WESTERN BLOT ANALYSIS**

Reagents and materials were obtained (from GE Healthcare, Uppsala, Sweden, unless otherwise indicated) for 2-dimensional electrophoresis experiments. Recent postmortem normal human retina (Michigan Eye Bank, Ann Arbor) was lysed (Cel-Lytic MT, 5mM Tris[2-carboxyethyl]phosphine hydrochloride), 1% protease inhibitor cocktail (Sigma-Aldrich, St Louis, Missouri) and centrifuged at 10,000g for 10 minutes at 4°C, and the supernatant was pooled. Protein (300 µg) was precipitated from the lysate (Amersham Clean-Up Kit, GE Healthcare). The pellets were incubated for 60 minutes at 30°C in 220 µL of isoelectric focusing rehydration buffer (7M urea, 2M thiourea, 1% amidosulfo betaine 14, 1% Triton X-100, 1%-[3-(cholamidopropyl)dimethylammonio]-1-propanesulfonic acid, and 1% immunohistologic investigations. The solubilized protein was loaded overnight onto 11-cm (pH 3-10) immobilized pH gradient strips using active rehydration at 50 V. Isoelectric focusing was performed at 40,000 V/h using isoelectric focusing Cell (BioRad Industries, Hercules, California). The focused IPG strips were equilibrated in buffers containing sodium dodecyl sulfate (SDS)-Tris (2-carboxyethyl)phosphine hydrochloride and SDS-todoacetamide. The second-dimension gels were run on 4% to 12% acrylamide Bis-Tris gels (BioRad Industries). After electrophoresis, duplicate gels were immunoblotted or stained with SYPRO Ruby (Molecular Probes, Eugene, Oregon).

Separated proteins were transferred onto nitrocellulose membranes and incubated with serum from patients having MAR and with horseradish peroxidase–conjugated mouse antihuman immunoglobulin as a secondary antibody. Immunoreactive spots on each membrane were compared visually and by using a computerized system. Each of the spots was matched to an equivalent spot on staining gels.

**IN GEL ENZYME DIGESTION AND MASS SPECTROMETRY**

Spots from 2-dimensional electrophoresis–stained gels were excised and in gel digested (Trypsin Gold; Promega, Madison, Wisconsin). Peptides were extracted from the gel plugs in 30 µL of 2% acetonitrile, 1% formic acid. Five microliters of alphanewydroxycinnamic acid (5 mg/mL in 50% acetonitrile, 0.1% trifluoroacetic acid [TFA], and 2 mM ammonium citrate) matrix was added to the digested peptides. The extracts were evaporated to dryness and then dissolved in 5 µL of 60% acetonitrile, 0.1% TFA. A 0.5-µL volume of this solution was spotted on a 192-well matrix-assisted laser desorption ionization target and allowed to dry.

Mass spectra were acquired using tandem time-of-flight mass spectrometry (4800 Proteomics Analyzer; Applied Biosystems, Foster City, California). Database searching was performed using commercially available software (GPS Explorer version 3.6, with Mascot version 2.1 against International Protein Index human version 3.32 using the following parameters: 30-ppm mass tolerance, 1 missed cleavage, carboxyamidomethyl (C) fixed modification, and variable modifications pyrroglut (N-term Q) and oxidation (M). Spectra were acquired in tandem mass spectrometry 2-kV–positive mode.

**IMMUNOBLOTS AND SDS–POLYACRYLAMIDE GEL ELECTROPHORESIS**

Retinal extract (20 µg of proteins), 0.1 µg of aldolase A, 0.1 µg of carbonic anhydrase II (CAII), 0.4 µg of aldolase C, 0.2 µg of recoverin, 0.2 µg of S-arrestin, 0.4 µg of S-transferase (GST) fusion α-enolase, and 0.2 µg of heat shock protein 60 (HSP60) were used. Samples were separated on 10% SDS–polyacrylamide gel electrophoresis gels. After electrophoretic run, immunoblot analysis was performed as described previously. We used GST fusion α-enolase (Abnova, Taipei, Taiwan) and aldolase A and HSP60 (Sigma-Aldrich). Bovine recombinant recoverin was purified as previously described. Human recombinant CAII was purified as previously described.

**IMMUNOHISTOCHEMISTRY**

Frozen sections were obtained from recent postmortem normal human retina (Michigan Eye Bank) embedded in optimum cutting temperature compound (Tissue-Tek; Miles Inc, Elkhart, Indiana). Sections were blocked for nonspecific protein binding with 5% goat serum in a phosphate-buffered saline (PBS) solution at room temperature for 1 hour and then
incubated with serum from patients with MAR (dilution, 1:500) overnight at 4°C. After washing with PBS plus 0.2% Triton X-100 (3 times at room temperature for 10 minutes each), the sections were incubated with Alexa Fluor 488–conjugated anti–goat IgG secondary antibody (dilution, 1:2000) (Molecular Probes). They were then counterstained with 4',6'-diamidino-2-phenylindole (0.3µM) before observation with a fluorescence microscope (Olympus, Tokyo, Japan).

RESULTS

IDENTIFICATION OF RETINAL AUTOANTIBODIES IN SERUM SAMPLES FROM PATIENTS WITH MAR

Proteomic analysis was performed of antigenic retinal proteins identified on Western blots. The identified MAR-
related antigenic retinal proteins are the same ones that have been identified in many CARs and AIRs cases, namely, antibodies against recoverin, α-enolase, S-arrestin, CAII, and HSP60.10,14,21 (Figure 1 and Table 1). We found 2 new antigenic retinal proteins on Western blots (aldolase C and aldolase A), which have not been reported in MAR, CAR, or AIR, to our knowledge. Immunoblot analysis of serum samples from patients with MAR using human, mouse, or bovine retinal extract, as well as purified proteins, found autoantibodies to recoverin (1 of 11), aldolase C (4 of 11), α-enolase (5 of 11), aldolase A (2 of 11), and HSP60 (11 of 11). Immunoblot analysis of 8 serum samples from patients with CAR and 9 control serum samples using purified proteins was also performed for comparison. Antibodies to recoverin (1 of 8) and aldolase A (1 of 8), and HSP60 (7 of 8) were identified in serum samples from patients with CAR, while antibodies to CAII, α-enolase, and aldolase C were not identified in serum samples from patients with CAR. Antibodies to CAII (1 of 9) and HSP60 (5 of 9) were identified in control serum samples, while antibodies to recoverin, S-arrestin, α-enolase, aldolase A, and aldolase C were not identified in control serum samples.

Some serum samples from patients with MAR did not show immunoreactivity on Western blots using solubilized normal retinal proteins, which led to development of the indirect immunohistologic method.8 Our investigations demonstrated immunoreactivity using both methods, with 9 of 11 patients having positive Western blots, 8 of 11 patients having positive immunohistologic reactivity, and 7 of 11 patients having both. Some patients with MAR have antibodies that are reactive with retinal cells other than bipolar cells, so the usefulness of bipolar cell staining as the sole basis for diagnosing MAR is limited to cases in which it occurs. Inner nuclear layer staining was common in our patients with MAR, but colocalization studies found bipolar cell staining in only 4 of 11 patients, while other inner nuclear layer retinal cells had focal immunoreactivity to patient serum (Figure 2). More detailed studies will be needed to elucidate the specificity of this immunoreactivity and to investigate other immunologic variables, as a few patients with MAR did not have reactive antiretinal antibodies by this method.

**Clinical Features of MAR**

To date, except for 2 case reports of choroidal melanoma,6,7 only MAR associated with cutaneous melanomas has been reported.3 We were surprised to find that any form of melanoma may potentially autosensitize the patient and lead to MAR. We examined 11 patients having MAR with the following types of melanoma: cutaneous (6 patients), choroidal tumors (2 patients), flat choroidal nevi (2 patients), and ciliary body (1 patient). Flat choroidal nevi usually are regarded as benign with little malignant potential unless there is demonstrated growth.22

![Table 1. Mass Spectroscopy Results for Each Western Blot Spot and Prevalence of Autoantibodies Found Against Each Retinal Protein in Melanoma-Associated Retinopathy (MAR), Cancer-Associated Retinopathy (CAR), and Control Serum](http://archophthalmol.com/127/12/1373/fig1.jpg)
However, the carcinogenic potential of flat choroidal melanomas seems to differ from their ability to serve as antigenic foci in autoimmune-susceptible individuals. Both of our patients with choroidal nevi (patients 1066 and 3361 in Table 2) had central scotomata, antiretinal antibodies, and severe ERG changes similar to the other patients with MAR. These 2 patients also had obvious degeneration of the retina at the margins of the nevi, and patient 1066 showed asymmetry of disease, which was worse in the eye with the large nevus (Figure 3). Four individuals (patients 322, 1066, 2052, and S49 in Table 2) with different forms of melanoma are shown as representative examples in Figure 3.

Clinically, the patients with MAR have similar findings, with rapid onset that included photopsias and loss of vision. Electroretinograms show retinal dysfunction (Figure 3) and aid in diagnosis of this condition with otherwise minimal retinal changes. Patients often have negative electroretinographic waveforms (a-waves and poor b-waves not reaching the isoelectric point) on dark-adapted maximal stimulation and central scotomata on visual field testing (Figure 3). In more advanced cases, patients develop retinal vessel attenuation and areas of diffuse atrophy. Retinal pigmentary changes are absent to minimal. We also found that patients with MAR commonly have personal and family histories of autoimmune disease, suggesting a special susceptibility for the putative retinal antigens released by their melanomas (Table 2). The latency from melanoma diagnosis to recognition of MAR ranged from 6 months to 14 years (median, 2 years) preceding the diagnosis. The trigger that set off the MAR response in the patients with longer latencies is unknown. One particularly intriguing individual with MAR (patient 175) with malignant melanoma of an amputated toe did not manifest MAR until after she had knee surgery in the same leg 5 years after amputation of the toe.

**COMMENT**

Typically, malignant melanoma is a highly invasive tumor derived from neuroectodermal melanocytes, which share a lineage with retinal cells. The molecular mechanisms underlying the development of MAR are unknown. Investigations of patients with MAR, CAR, and AIR frequently show positive family histories for autoimmune diseases, and many patients have autoimmune genetic templates that increase their susceptibility to autoimmune diseases. Examination of tumors in pa-
The retina, S-arrestin and recoverin have important roles in regulating the expression of these proteins in the carcinomas is unknown. In this study, we identified 7 different autoantibodies against S-arrestin, recoverin, aldolase C, HSP60, and CAII. We did not have access to the mRNA level, and autoantibodies against these proteins were detected by SEREX (serological expression of antigens) analysis.

Table 2. Findings in 11 Patients With Melanoma-Associated Retinopathy (MAR)

| Patient No./Sex/Age, y | Tumor Type | Time From Malignant Melanoma Diagnosis to Recognition of MAR | Personal or Family History of Autoimmune Disease | Visual Acuity | Retinal Appearances | Goldmann Visual Fields | % Mixed Response (Ratio of b-Waves to a-Waves) Photopic Response | Rod-Isolated Response | Carboxic Anhydrase II | S-Arrestin | α-Enolase | Aldolase A | Heat Shock Protein 60 | Staining Location With Serum |
|----------------------|------------|----------------------------------------------------------|-----------------------------------------------|---------------|---------------------|------------------------|-------------------------------------------------|---------------------|------------------|-----------------|----------|----------|-----------------|-----------------------------|-----------------------------|
| 175/F/75             | Malignant melanoma, R toe amputated 1998, R knee surgery 27 | MAR 2004 | DM (sister), lupus (daughter), fibromyalgia (daughter) | CF OU | Granular pigmentation of macular OU | 5-Degree central scotoma with enlarged blind spots OU | 0.5 | Negative, 46 OD; 0.5, negative, 48 OD | + | + | + | + | + | INL inner plexiform layer |
| 317/F/85             | Choroidal nevus | Choroidal 14 y | Unknown | 20/25 OD, enucleated OS | Diffuse retinal and retinal pigment epithelial atrophy OD | Constricted peripheral fields (4-4° isopter constricted to 15 degrees) OD | 0.5 | Negative, 40 OD | + | + | + | + | + | INL |
| 322/M/58 Ciliary body | Concurrent | None | 20/20 OU | Generalized depigmented fundus with focal pigment deposits OU | Paracentral scotoma OD, partial ring scotoma OS | 13 OD, 10 DS | 1.3, Near negative, 29 OD; 1.0, negative, 24 DS | + | + | + | + | + | No staining |
| 471/M/50 Cutaneous | Metastatic cutaneous | 6 mo Before melanoma diagnosis | Ulcerative colitis and arthritis (patient), asthma (mother) | 20/40 OU | Posterior pole subretinal exudation OU | Full fields | 63 OD, 79 DS | 1.7, 81 OD, 1.5, 87 DS | + | + | + | + | + | Cone inner segments INL |
| 886/F/72             | Cutaneous | 3 y | RA (patient) | 20/80 OD, 20/100 OD | Retinal atrophy at macular and posterior pole RPE mottling OU | Central scotoma OU (5-degree scotoma OU) | 31 OD, 41 DS | 1.2, Negative, 36 OD; 1.3, near negative, 44 OD | + | + | + | + | + | INL |
| 1086/M/68 Choroidal nevus | Concurrent | RA (mother, sister), DM (father), thyroid disease (daughter) | 2/200 OD, 20/200 OD | Large choroidal nevus with surrounding choroidal atrophy OD, peripheral retina/RPE atrophy OS | Temporal island of vision only OD, ring scotoma with constriction of peripheral field to 50 degrees (10°) | 11 OD, 34 DS | 0.1 OD, 0.1, negative, 3 OD | + | + | + | + | + | INL GCL |

Patients manifesting CAR have demonstrated ectopic expression of retinal antigens, which are recognized as foreign by the immune system and lead to initiation of an immune response.1 In this study, we identified 7 different anti-S-arrestin antibodies in our patients with MAR against S-arrestin, recoverin, α-enolase, aldolase A, aldolase C, HSP60, and CAII. We did not have access to the patients’ neoplasms to evaluate the presence of retinal proteins in the tumors.

S-arrestin expresses in melanoma cell lines at the messenger RNA level, and autoantibodies against these proteins were detected by SEREX (serological expression of cDNA expression libraries) in the serum of patients with melanoma.25 Recoverin, a Ca2+-binding regulatory protein, is present in retinal photoreceptor and bipolar cells20 and is considered a major antigen involved in the immunopathogenesis of CAR.23 Recoverin is aberrantly expressed in carcinoma13 and melanoma cells.24 The function of these proteins in the carcinomas is unknown. In the retina, S-arrestin and recoverin have important roles in phototransduction.27 Enolase is a ubiquitous enzyme that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate and generates adenosine triphosphate in glycolysis.28 α-Enolase was found to be present in central nervous system neurons34 and in human A375 melanoma cells.29 Autoantibodies against α-enolase are often associated with progressive visual loss in patients with CAR and noncancer (nonparaneoplastic) AIR; results of studies24,30 suggest that they have a pathologic role in retinopathy. Anti-α-enolase autoantibodies have been shown to have a role not only in systemic and invasive autoimmune disorders31 but also in some cancerous diseases.32 To our knowledge, this is the first report that serum from patients with MAR commonly (5 of 11) contains anti-α-enolase antibodies. The present study confirms that autoantibodies against S-arrestin, recoverin, α-enolase, and CAII occur in many patients with MAR.32 Anti-HSP60 antibody was found in patients with MAR and in control serum samples.

Aldolase is a glycolytic enzyme that catalyzes the reversible conversion of fructose-1,6-bisphosphate to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate. The following 3 isozymes of aldolase occur in vertebrates: aldolase A (the major form in muscle),34...
Table 2. Findings in 11 Patients With Melanoma-Associated Retinopathy (MAR) (continued)

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<tr>
<th>Patient No./Sex/Age</th>
<th>Tumor Type</th>
<th>Time From Malignant Melanoma Diagnosis to Recognition of MAR</th>
<th>Personal or Family History of Autoimmune Disease</th>
<th>Visual Acuity</th>
<th>Retinal Appearance</th>
<th>Goldmann Visual Fields</th>
<th>Mixed Response (Ratio of b-Waves to a-Waves)</th>
<th>Photopic Response</th>
<th>Carbonic Anhydrase II</th>
<th>S-Arrestin</th>
<th>α-Enolase</th>
<th>Aldolase A</th>
<th>Aldolase C</th>
<th>Heat Shock Protein 80</th>
<th>Staining Location With Serum Antibodies</th>
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<tbody>
<tr>
<td>1066/M/88 Choroidal nevus</td>
<td>Concurrent RA (mother, father)</td>
<td>2002 OD, 20/20 OS</td>
<td>Large choroidal nevus with surrounding chorioretinal atrophy OD, peripheral retina/RPE atrophy OS</td>
<td>Temporal island of vision only OD, ring scotoma with constriction of peripheral field to 50 degrees (IV-4-e) OS</td>
<td>NR OD</td>
<td>1.1, negative, 3 OS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Aldolase A</td>
<td>Aldolase C</td>
<td>Heat Shock Protein 80</td>
<td>INL GCL</td>
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<tr>
<td>1099/F/78 Cutaneous</td>
<td>2 y</td>
<td>Treated with hydroxychloroquine sulfate (patient)</td>
<td>20/400 OU</td>
<td>Scalloped retinal, RPE atrophy posterior pole with peripheral pigment OU</td>
<td>Mideripheral islands of vision to IV-4-a isopter OD, midperipheral interfoveal island of vision to IV-4-a isopter OS</td>
<td>NR OU</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>No staining</td>
<td></td>
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<tr>
<td>2002/F/83 Cutaneous</td>
<td>11 y</td>
<td>RA (patient)</td>
<td>20/20 OU</td>
<td>Crescentic depigmentation temporal to macular and peripheral retinal atrophy OU</td>
<td>Paracentral scotoma OU</td>
<td>20 OD; 12 OS</td>
<td>76 OD; 42 OS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>No staining</td>
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<tr>
<td>2052/F/44 Cutaneous</td>
<td>3 y</td>
<td>RA (patient)</td>
<td>20/80 OD, 20/50 OS</td>
<td>Macular retinal atrophy OU</td>
<td>Paracentral scotoma OU</td>
<td>NR OU</td>
<td>0.8, Negative, 0.0; 0.8, negative, 0.8 OS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>INL</td>
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<td>3361/F/82 Choroidal nevus</td>
<td>Concurrent RA, asthma, Sjögren syndrome (patient); DM (mother, father, brother)</td>
<td>2060 DD, CF OS</td>
<td>Interperipher nevus with surrounding chorioretinal atrophy OS, generalized retinal/RPE atrophy OU</td>
<td>Paracentral scotoma OD, central scotoma OS, moderate constriction of peripheral field OU</td>
<td>NR OU</td>
<td>NR OU</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>INL GCL</td>
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<tr>
<td>549/M/73 Choroidal nevus</td>
<td>Arthritis treated with prednisone (patient)</td>
<td>Enucleated OD, 20/125 OS</td>
<td>Generalized retinal atrophy OS</td>
<td>Central 20-degree scotoma OS</td>
<td>40 OS</td>
<td>1.5, Near negative, 45 OS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Cone INL</td>
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Abbreviations: CF, counting fingers; DM, diabetes mellitus; GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; NR, not recordable; RA, rheumatoid arthritis; RPE, retinal pigment epithelium; ellipsis, not applicable.

* Percentage of mean normal (age 20-60 years) was used as a reference to grade the severity of dysfunction. Negative indicates a negative waveform in which the b-wave does not return to the isoelectric baseline, and near negative indicates that the b-wave generated is marginally above the isoelectric baseline.

* Plus sign indicates presence.
or absence of these markers with clinical data. The diversity of autoantibodies produced in MAR may be the consequence of varied overexpression among retinal proteins involved in melanoma tumor development, as well as among these patients’ propensity to develop autoimmune autoantibodies.14 In general, AIR is treatable with immunosuppression therapies,11,18 but no standardized protocols have been established. In addition, it is unknown whether the antibodies that develop in patients with MAR may have a therapeutic role in retarding tumor growth.

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REFERENCES

1. Sawyer RA, Selhorst JB, Zimmerman LE, Hoyt WF. Blindness caused by photo- 
81(5):606-613.

2. Suhler EB, Chan CC, Caruso RC, et al. Presumed teratoma-associated para-neo-

3. Saito W, Kase S, Ohguro H, Furudate N, Ohno S. Slowly progressive cancer-


5. Keltner JL, Thirkill CE, Yip PT. Clinical and immunologic characteristics of mela-
noma-associated retinopathy syndrome: eleven new cases and a review of 51 

6. Zacks DN, Pinnolis MK, Berson EL, Gragoudas ES. Melanoma-associated reti-

7. Nieuwendijk TJ, Hooymans JM. Paraneoplastic vitelliform retinopathy associ-

8. Milam AH, Saari JC, Jacobson SG, Lubinski WP, Feun LG, Alexander KR. Auto-
antibodies against retinal bipolar cells in cutaneous melanoma-associated reti-

9. To KW, Thirkill CE, Jakobiec FA, Lessell S, Berson EL. Lymphoma-associated 
rhinophotophobia: a photoreceptor-specific calcium-binding protein, is expressed by the tu-
mor of a patient with cancer-associated retinopathy. Proc Natl Acad Sci U S A. 

10. Adamus G, Hertzig D, Weleber RG. Autointibodies against retinal proteins in para-


14. Singh AD, Mokashi AA, Bena JF, Jacques R, Rundle PA, Rennie IG. Small cho-
113(6):1032-1039.

(6668):632-633.

16. Sawyer RA, Selhorst JB, Zimmerman LE, Hoyt WF. Blindness caused by photo-
81(5):606-613.

17. Suhler EB, Chan CC, Caruso RC, et al. Presumed teratoma-associated para-

18. Potter MJ, Thirkill CE, Dam OM, Lee AS, Milam AH. Clinical and immunocy-


20. Heckenlively JR, Apteisaruri N, Holder G. Autoimmune retinopathy, CAR and MAR 

21. Ferreyra HA, Jayasundera T, Khan NW, He S, Lu Y, Heckenlively JR. Manage- 

calcium sensor in vision. Proc Natl Acad Sci U S A. 1992;89(13): 
5705-5709.

23. Nair SK, Calderone TL, Christianson DW, Fierce CA. Altering the mouth of a hy-
drophobic pocket: structure and kinetics of human carbonic anhydrase II mu-


25. Feng Y, Yao KW. Phototransduction in mouse rods and cones. Plfugers Arch. 2007; 
454(5):803-819.


27. Clauser KR, Hall SC, DM, et al. Rapid mass spectrometric peptide sequence-
ning and mass matching for characterization of human melanoma proteins isolated 
by twodimensional PAGE. Proc Natl Acad Sci U S A. 1995;92(11): 
5072-5076.

28. Weleber RG, Watzke RC, Shults WT, et al. Clinical and electrophysiological char-
acterization of paraneoplastic and autoimmune retinopathies associated with 

29. Giffits VM, Toh BT, Snytr DW. Disease association, origin, and clinical rele-
vance of autointibodies to the glycolytic enzyme enolase. J Investig Med. 2001; 
49(2):138-145.

WA. Serum antibodies to retinal antigens in lung cancer and sarcoidosis. 

31. Haapasalo J, Nordfors K, Järvell S, et al. Carbonic anhydrase II in the endothe-
308-313.

32. Ujafi K, Kitajima I, Kato K, Shimizu C, Nakajima T, Maruyama I. Serum samples of patients with rheumatoid arthritis contain a specific autoantibody to “dena-
tured” aldolase A in the osteoblast-like cell line. MG-63. Ann Rheum Dis. 1999; 

33. Tsutsumi K, Ito K, Ishikawa K. Developmental appearance of transcription fac-

regional expression of the rat aldolase C gene in the central nervous system of 

35. Caffe AR, Von Schantz M, Szel A, Vood K, Van Veen T, Distribution of Purkinje 
and cell-specific Zebrin-II/aldolase C immunoreactivity in the mouse, rat, rabbit, 


WA. Serum antibodies to retinal antigens in lung cancer and sarcoidosis. 

38. Haapasalo J, Nordfors K, Järvell S, et al. Carbonic anhydrase II in the endothe-
308-313.

and cell-specific Zebrin-II/aldolase C immunoreactivity in the mouse, rat, rabbit, 


41. Caffe AR, Von Schantz M, Szel A, Vood K, Van Veen T, Distribution of Purkinje 
and cell-specific Zebrin-II/aldolase C immunoreactivity in the mouse, rat, rabbit, 