PARANEOPLASTIC RETINOPATHIES AND OPTIC NEUROPATHIES VS. (NON-CANCER) AUTOIMMUNE RELATED RETINOPATHY AND OPTIC NEUROPATHY (ARRON SYNDROME)

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LEARNING OBJECTIVES
1. The audience shall have gained an understanding of paraneoplastic retinopathies and optic neuropathies.
2. The audience should have an understanding of a non-paraneoplastic autoimmune related retinopathy and optic neuropathy.
3. The audience should be able to distinguish between these entities and what treatment modalities may be available.

CME QUESTIONS
1. For patients with cancer-associated retinopathy, all of the following are true except one:
   a. They typically have a severely reduced ERG
   b. They usually display a marked loss of vision
   c. They often have photopsias
   d. Small cell carcinoma of the lung is one of the more common associated tumors
   e. The visual loss is easily treated with appropriate immunologic therapy
2. All of the following are true about melanoma-associated retinopathy except one:
   a. The ERG shows a markedly reduced B wave, with a normal A wave
   b. Flickering photopsias are common
   c. The treatment of MAR syndrome is never helpful
   d. The condition normally affects males
   e. Central vision acuity may be normal or show severe reduction
3. Patients with autoimmune related retinopathy and optic neuropathy (ARRON Syndrome) have all the following characteristics except one:
   a. May be responsive to steroid therapy
   b. May have other systemic autoimmune diseases
   c. May have an abnormal ERG as well as optic atrophy
   d. Can have a prolonged course of visual loss
   e. Their visual loss may be associated with cancer

KEY WORDS
1. AIR Syndrome
2. ARRON Syndrome
3. CAR Syndrome
4. DUMP Syndrome
5. MAR Syndrome
6. PON Syndrome

INTRODUCTION
This lecture will cover the following topics:
1. Terminology used for Autoimmune Retinopathy and Optic Neuropathy
2. Antiretinal Antibody Detection and Measurement
3. Cancer Associated Retinopathy (CAR Syndrome)
   a. Cancer Associated Cone Dysfunction (CAC Syndrome)
4. Paraneoplastic Optic Neuropathy (PON Syndrome)
5. Diffuse Uveal Melanacytic Proliferation (DUMP Syndrome)
6. Melanoma Associated Retinopathy (MAR Syndrome)
7. Autoimmune-related Retinopathy & Optic Neuropathy (ARRON Syndrome)
   a. Nonparaneoplastic Retinopathy with Cystoid Macular Edema (npAIR/CME= ARRON/CME)

1. Terminology
The terminology used to describe autoimmune retinopathy and optic neuropathy has been confusing. The confusion is related to the fact that the various autoimmune syndromes are not well defined in terms of specific immunologic and etiopathogenesis. We favor the terms used in the introduction above. In addition the terms AIR (Autoimmune retinopathy) has been used to describe patients with both cancer and non cancer. AIR is then subdivided into CAR Patients and nonparaneoplastic AIR (npAIR). There is a group of npAIR patients who have cystoid macular edema (npAIR/CME). Also the term AR (Autoimmune Retinopathy) has been used by Adams to describe nonparaneoplastic autoimmune retinopathy patients. The problem with the terms both AIR and AR is that they do not consider that many of these syndromes...
may include optic nerve abnormalities with optic atrophy and antibodies to the optic nerve. Thus, we favor the term ARRON Syndrome (Autoimmune-related retinopathy and optic neuropathy). The term “autoimmune-related” is used rather than simply “autoimmune” because it is unclear whether, in all cases, the antibodies that are generated from the retina and optic nerve are part of the etiology of the visual loss, or whether they truly represent an epiphenomenon to non-specific breakdown of retinal and optic nerve proteins. We now recognize from the work of Heckenlively that some cases of ARRON may have cystoid macular edema and we would call these ARRON with CME. ARRON/CME is discussed in much greater detail later in this lecture under ARRON Syndrome.

2. Antiretinal Antibody Detection and Measurement
Various autoimmune syndromes are not well defined in terms of immunologic and genetic abnormalities that define these syndromes. The more we learn about these autoimmune syndromes the more complex is the information discovered. We and others have found that the normal human serum contains many antibodies to retina and optic nerve. Forooghian et al has written of the need to standardize the detection and measurement of antiretinal antibodies. The authors discuss the use of Immunohistochemistry, Western blot, and Enzyme-Linked Immunosorbent Assay: ELISA in defining these syndromes. We agree completely with the concepts in the paper. We have used serum from over 100 normal controls for comparison of patients with possible autoimmune syndromes evaluating antibodies against both retina and optic nerve. Adamus has established a clinical testing laboratory (Laboratory Improvement Amendments (CLIA) Certification) in 2005 for testing antiretinal antibody and anti-optic nerve autoantibody by Western blotting and immunohistochemistry. However, despite these advancements we agree with Forooghian understanding of these syndromes from an immunologic and probably genetic standpoint is still in its infancy. The need for standard assays and multicenter collaborations will be essential to our understanding and defining of these various syndromes. Western Blot Techniques (WB) using human tissue to study retina and optic nerve is ideal, but while some investigators have found fresh human tissue not hard to obtain, it has often been difficult in other laboratories to get fresh human retina and optic nerve. We have found pig optic nerve and retina works well and correlates well with human tissue using Western Blot Techniques. Others have found human tissue alongside mouse and bovine retinal tissue works well.

While we feel it is important to diagnose and treat these various syndromes using immunologic techniques, we realize that in the diagnosis of these various syndromes the clinician cannot use immunology alone. The clinical conditions must be strongly correlated to make the appropriate diagnosis. In addition to treat these various syndromes while ideally the clinician would like to see the antibody titer reduced, we recommend that clinical parameters (including visual acuity, visual fields, color vision, ERG, OCT, and sometimes VEP) are the key to monitoring all these syndromes.

3. CAR and CAC Syndromes
Cancer-associated retinopathy (CAR syndrome) describes a visual paraneoplastic disorder generally associated with small cell carcinoma of the lung, usually containing antibodies against retinal elements and causing both rod and cone dysfunction. Often associated with photopsias, visual loss occurs usually over months and frequently precedes the discovery of cancer. Clinical difficulties associated with cone dysfunction include photosensitivity, abnormal visual acuity, color vision abnormalities, central scotomas and an abnormal cone-mediated electroretinogram (ERG). Clinical problems associated with rod dysfunction include nyctalopia, prolonged dark adaptation, peripheral or ring scotomas and an abnormal rod-mediated ERG. CAR has been rarely reported to be slowly progressive.

Blindness as a remote effect of cancer was first recognized and described in 1976 by Sawyer et al, followed by Keltner, Roth and Chang, who presented the next report of paraneoplastic retinopathy at the 1981 Walsh Society Meeting, describing a patient with cancer-associated vision loss (Keltner JL, Roth AM and Chang RS, unpublished data, 1981). The authors proposed, in that presentation, the autoimmune theory of cancer-induced blindness based upon the patient’s response to steroids as well as the demonstrated anti-retinal antibodies seen primarily reacting against photoreceptor cells. These findings were subsequently published in 1983. They confirmed the work of Kornguth et al who demonstrated anti-retinal ganglion cell antibodies in patients with small cell carcinoma of the lung. The isolation of the 23 kd CAR retinal antigen was first reported by Thirkill et al in 1987. The first recognition of the 23 kd antigen as the photoreceptor component recoverin was by Thirkill et al in 1992. In that article, Thirkill et al showed that the nucleic acid sequence of a cDNA cloned from the library of human retina exhibited 90% homology with that of the bovine counterpart. They subsequently published in 1993 by Polans et al.

Addressing the question of sensitization, Thirkill et al in 1993, 1996, and 1997 found intraperitoneal cultivation of small cell carcinoma induced expression of relevant cancer associated retinopathy antigens while others described the expression of recoverin in biopsies of small cell carcinomas from patients with CAR.

Several examples of small cell carcinomas actively expressing recoverin have been described and are considered responsible for the induction of the autoimmune attack on the retina of patients with the 23 kd CAR Syndrome. If autoimmunity is responsible for the vision loss in CAR patients, this immunologic cancer connection represents the most likely trigger mechanism.
With respect to expression of retinal proteins by cancers, the gene for mouse recoverin protein 23 kd was assigned to the mouse chromosome 11, closely linked to Trp53. While the human recoverin gene was mapped to the human chromosome 17 by Murakami et al. in 1992, it was shown by Freund et al. and McGinnis et al. to be localized at position 17p 13.1, a region containing a number of cancer–related loci. This suggests a possible mechanism for the aberrant expression of recoverin, which results in sensitization to this 23 kd photoreceptor component. McGinnis et al. proposed a hypothesis for CAR retinopathy as a single mutational event that inactivates a copy of the p53 tumor suppressor gene which turns on the synthesis of a recoverin protein with the cell line becoming cancerous because of the tumor’s loss of the suppressor activity of the p53 protein. Thus, synthesis of the recoverin epitopes outside the eye accounts for production of circulating antibodies against recoverin which may inactivate recoverin with closure of the ion channels and depolarization of cells sufficient to kill the photoreceptors. McGinnis et al. also felt that the event might be a deletion or the translocation with joining of the recoverin sequence to an active gene.

The underlying mechanism involved in the CAR syndrome, as in other paraneoplastic retinopathies, is probably related to molecular mimicry. According to this mechanism, paraneoplastic retinopathies occur when susceptible individuals produce immune response to a cancer antigen which cross-reacts inappropriately with a retinal protein. Anti–recoverin antibodies appear to bind with the target molecules in the retina to cause apoptotic cell death. Anti–recoverin antibodies probably block the function of recoverin which regulates rhodopsin phosphorylation in a calcium–dependent manner. Certain cancers produce a recoverin protein aberrantly expressed in the cancer tissue which is recognized by the immune system of the patient. The secondary anti–recoverin antibody then reaches the retina and is taken into the photoreceptor cell. It is felt that the antibody blocks the recovery function and enhancement of rhodopsin phosphorylation to induce the retinal apoptosis. Adamus et al. have demonstrated that anti–recoverin induces an increase in intracellular calcium, leading to retinal cell death via a mitochondrial apoptotic pathway. In addition, nifedipine has been found to protect against anti–recoverin induced apoptosis.

Retina proteins other than the 23 kd recoverin are implicated in the CAR syndrome, revealing a collection of potential autoantigens distributed throughout the neurosensory retina, with active counterparts in the brain. In our experience, the 23 kd recoverin protein is still the most common antigen linked with cancer–associated retinopathy. The next most common retinal antigen antibody reactions appear to be those involving a 40 kd protein followed by 45 kd and 60 kd proteins, none of which have been cloned to provide the exact protein sequence of the retinal antigen involved. It is relevant to note that over 20 antigens have been described in the CAR syndrome distributed throughout the retina (in rods, cones, ganglion cells and other various retinal components) and in the optic nerve. Table 1.

Ohguro reported that aberrant expression of recoverin was identified in more than 50% of tumor cells from several types of cancer including gastric, lung and other cancers. Their data showed that recoverin–expressing cancer cells induced tumor immunity and provided a favorable prognosis for primary cancer in CAR patients.

Peek has reported that in two CAR patients the 40 kd protein was located to the photoreceptors and a 35 kd protein was located in the outer plexiform layer.

Misiuk-Hojio reported in a screening of 295 patients with diagnosed breast cancer that 6 out of 295 patients (2%) had high–titer of antibodies to retinal antigens. These patients underwent an ophthalmic and neurologic exam and were found to have symptoms of CAR.

Querques reported the third case of CAR associated with invasive thymoma and first case reported with antibodies to a 145 kd protein believed to interphotoreceptor retinoid–binding protein (IRPB) and choroidal neovascularization.

Table 1.

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<tr>
<th>Non 23Kda Paraneoplastic antigens to retina and/or optic nerve</th>
<th>Resources</th>
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<tr>
<td>24Kda</td>
<td>32</td>
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<td>26Kda</td>
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<td>45Kda</td>
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<td>46Kda (Anti-enolase)</td>
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<td>60Kda</td>
<td>38</td>
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<tr>
<td>62Kda (CRMP-5)</td>
<td>37,81,85</td>
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<td>65Kda</td>
<td>21</td>
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<tr>
<td>70Kda</td>
<td>21</td>
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<td>Anti-ganglion cell antibodies and anti-neurofilament (70Kd, 145Kd, 205Kd)</td>
<td>10,14,15</td>
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<tr>
<td>Anti-hsc70</td>
<td>189,190</td>
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<tr>
<td>TULP1 - (Tubby-like protein)</td>
<td>75,191</td>
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<tr>
<td>PRN (Photoreceptor cell–specific nuclear receptor gene product)</td>
<td>192-194</td>
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<td>PTB</td>
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Retinal enolase, the 46 kd protein, has also been associated with CAR syndrome. However, Gitlits et al reported the presence of enolase in a patient with discoid lupus erythematosus and showed enolase autoantibodies in two patients without systemic disease, suggesting that enolase autoantibodies have a broad association and are not restricted to any particular disease.

There are numerous types of malignancies associated with CAR. The most common cause for CAR syndrome is small cell carcinoma of the lung. The next most common is uterine cancer including endometrial and cervical cancer. They are followed by lymphoma, prostate cancer, laryngeal cancer, colon cancer, pancreatic cancer, undiagnosed cancers and metastatic cancers from unknown cause.

Treatment modalities used in the CAR syndrome as well as non-CAR autoimmune retinopathy and optic neuropathy include: 1) treatment of the underlying primary cancer; 2) prednisone; 3) plasmapheresis; and 4) intravenous immunoglobulin (IVIg). Monitoring anti-retina titers in response to immunomodulation can prove useful in patient management. Monitoring antibody titers demonstrates whether immunosuppressant therapy is controlling the autoimmune process. If a titer does not fall to baseline level, other immunosuppressant measures may be necessary. There is concern that reducing the antibody response could increase cancer mortality, however, we are unaware of any documented example. However, monitoring anti-retinal titers may not be practical. Thus, it becomes necessary to following as many objective parameters of visual function as possible to tell if visual loss has stabilized. Visual acuity, visual fields and color vision are the easiest to follow. Also, ERG testing is necessary. Thus, appropriate clinical history, examination, electrophysiologic findings, and immunologic testing are necessary to diagnose the CAR syndrome and separate it from other non-cancer-associated autoimmune retinopathies. It is important to appreciate that cancer-associated retinopathy and recoverin-associated retinopathy may be related entities, the understanding of which is currently evolving.

The recent upsurge of interest into the immunologic aspects of vision loss in non-cancer patients and cancer patients supports evidence of autoimmune involvement in associated retinopathies. Recent presentations by Heckenlively et al and Aptsiauri et al demonstrated patients with progressive panretinal degeneration from such conditions as idiopathic retinopathies and retinitis pigmentosa who had CAR-like clinical changes in association with the presence of antibodies to recoverin and other retinal proteins. Further research into this group of cancer–related and non-cancer–related retinopathies may lead to basic understandings of visual loss associated with a variety of retinal degenerations.

The diagnosis of CAR syndrome cannot be made by testing for a single antigen. More extensive immunologic testing is necessary. Thus, appropriate clinical history, physical and ophthalmologic examination, laboratory examination, electrophysiologic findings, and immunologic testing are necessary to diagnose the CAR syndrome and separate it from other non-cancer–associated autoimmune retinopathies. It is important to understand the CAR syndrome and separate it from other non-cancer–associated autoimmune retinopathies.

Cancer Associated Cone Dysfunction (CAC Syndrome) is a subset of CAR Syndrome wherein antibodies are primarily directed against cones. By contrast, CAC patients have photophobia, loss of color perception, central scotomas, and an ERG showing a reduction in the cone responses. Cogan described the first case of this in 1990. An unusual case of cone dysfunction was described by Jacobson and Thirkill with the presence of 23Kd and 50Kd antibodies. Campo et al, described a small cell carcinoma of the endometrium with an ERG showing decreased cone response. Parc reported a 50 year–old woman with CAC and abnormalities restricted to cone dysfunction with laryngeal carcinoma. The serum from this patient had two retinal antigens approximating 40 Kd that localized to the outer segments of the photoreceptor layer.
4. Paraneoplastic Optic Neuropathy

Paraneoplastic Optic Neuropathy is rare syndrome less commonly diagnosed than the CAR syndrome. However, to completely separate them is probably incorrect since it is known that there may be antigens which cross-link both in the optic nerve and retina. Paraneoplastic optic neuropathy is a subacute, progressive, frequently bilateral painless loss of vision, however it can present with acute visual loss.59,81-84 The important diagnosis to eliminate is that the patient does not have direct compression or infiltration of the optic nerve. Pathologic findings have shown non-specific vascular infiltration by lymphocytes as well as delimitation of the axons.26,40,85-86 Associated findings in patients with PON include cranial nerve palsies, polyneuropathy, vertical or downbeating nystagmus, as well as cerebellar signs.

Paraneoplastic optic neuropathy can also be associated with a subacute cerebellar syndrome. Most of these patients have a serum antibody specific for a recently defined 62 Kd neuronal antigen named collapsing response–mediating protein–5 (CRMP–5).85 Yu et al85, described the paraneoplastic IgG autoantibody, a neuronal cytoplasmic protein, a previously unknown 62 Kd member of the CRMP family. Since 1993 they have seen 121 cases in their laboratory. They believe that CRMP–5 is as frequent as PCA–1 (anti–Yo) autoantibody, and second in frequency only to ANNA–1 (anti–Hu). Other neurological signs revealed in clinical information of 116 patients were high frequencies of chorea (11%) and cranial neuropathy (17%, which includes 10% loss of olfaction/taste, and 7% optic neuropathy). Additional common signs were peripheral neuropathy (47%), autonomic neuropathy (31%), cerebellar ataxia (26%), subacute dementia (25%), and neuromuscular junction disorders (12%). Spinal fluid was inflammatory in 86%. In 37% of cases, the level of spinal fluid CRMP–5 IgG either equaled or significantly exceeded serum titers. Lung carcinoma (mostly limited small–cell) was discovered in 77%, thymoma in 6%. Half of the remaining patients had miscellaneous neoplasm (all but two were smokers). In all cases, serum IgG bound to CRMP–5 (mostly N–terminal epitopes), but not to human CRMP–2 or –3. Yu et al85, have proposed that in all likelihood, the anti–CV2 autoantibody is CRMP–5 specific.

Dr. Shelly Cross presented at NANOS a subset of patients with CRMP–5–IgG. 172 patients presented with subacute neurologic disorders. Fifteen patients had optic neuritis with retinitis documented in five. The fifteen optic neuritis patients were age 52–74 and were smokers; 8 were female. Fourteen had subacute visual loss and field defects. Four out of 4 tested had abnormal ERGs; vitreous cells were seen in nine. Two patients with myelopathy and optic neuritis bore a superficial resemblance to Devic’s disease. Other neurologic abnormalities included change in mental status, cranial neuropathies, movement disorders, myelopathy, peripheral nerve disorders, cerebellar and autonomic dysfunction. Small–cell lung carcinoma was confirmed in 10 patients, the remaining 5 had another carcinoma or provisional evidence for lung cancer.87 CRMP–5–IgG was detected at 1:1,000 to 1:500,000 dilution. No serum had CAR–IgG. Vitrectomy revealed reactive lymphocytosis (4/4) (the one case test was predominantly CD4+). Western blots demonstrated full–length CRMP–5 protein in optic nerve retina. Peroxidase staining revealed cytoplasmic immunoreactivity in retinal ganglion cells, nerve fiber layer and photoreceptor cells.87 Thus, Dr. Cross and associates have identified CRMP–5–IgG, a novel paraneoplastic ophthalmic process of combined optic neuritis and retinitis accompanied by vitreal inflammation.87 Margolin reported on CRMP–5 PON and vitritis as the only clinical manifestation in a patient with small cell lung carcinoma.88 Isolated cases of PON without other CNS pathology are rare. There appear to be only four cases of isolated CRMP–5 reported.89-92 There appears to be only two cases of CRMP–5 PON to report neuropathologic findings.91,93 We recently had a case of isolated PON with breast cancer with a 22Kd protein against both optic nerve and retina and no evidence of CRMP–5. She was diagnosed with breast cancer and had a remote history of lung and cervical cancer. The patient while initially responding to treatment for her visual loss eventually had progressive visual loss and died of her breast cancer.

Bilateral optic neuropathy and subacute ataxia were manifestations of a paraneoplastic neurologic disorder in a woman found to have a small cell carcinoma of the lung. Serologic tests revealed a neuronal autoantibody specific for CRMP–5, a 62 Kd member of the collapsing response–mediating protein family. Unexplained optic neuropathy in the setting of subacute cerebellar ataxia should cause suspicion of a paraneoplastic disorder and prompt testing for this autoantibody, especially in patients at risk for lung carcinoma.91 Treatment of paraneoplastic optic neuropathy results have been highly variable but can result in visual improvement.59,85-86,94-99

5. Diffuse Uveal Melanocytic Proliferation (DUMP Syndrome)

What has been called the bilateral diffuse uveal melanocytic proliferation (DUMP) syndromes characterized by bilateral progressive cataracts, iris masses, choroidal melanocytic proliferation, and overlying detachment associated with a cancer. This is a rare disorder with associated ocular features which include: round or oval, subtle red patches at the level of the retinal pigmented epithelium in the posterior fundus with early hyperfluorescence on fluorescein angiogram corresponding to these patches; multiple, slightly elevated pigmented and non–pigmented uveal melanocytic tumors involving the iris; diffuse thickening of the uveal tract; exudative retinal detachment; and rapidly progressive cataracts. This is generally associated with a systemic cancer which may not be recognized at the time of the ocular symptoms. This usual progresses in a rapidly fatal fashion.100

Approximately 25 cases have been reported in the literature100-120, with 23 involving malignant tumors. The average survival from initial presentation was 16.8 months. Three patients survived without recurrence for...
13, 17, and 68 months. Retention of visual acuity is poor, but intervention with corticosteroids, ocular surgery, chemotherapy and radiotherapy can be helpful.\textsuperscript{100} Saito has reported a case of DUMP associated with CAR.\textsuperscript{121}

Tumors that have been associated with DUMP Syndrome include ovarian cancer, lung cancer, uterine cancer, colon and rectal cancer, as well as metastatic cancer from unknown causes. O’Neal reported a case of pancreatic carcinoma in DUMP.\textsuperscript{122} Duong has reported a case of DUMP with ovarian carcinoma and metastatic amelanotic melanoma.\textsuperscript{123} Males and females appear to be equally affected. Visual loss often precedes the cancer from months to years.\textsuperscript{100}

Differential diagnosis in DUMP Syndrome include idiopathic uveal effusion; posterior scleritis; Vogt–Koyanagi–Harada syndrome; sarcoidosis; infectious granulomatous conditions; acute posterior multi–focal placoid pigment epitheliopathy (AMPPE), and sympathetic uveitis. Neoplastic disorders which may mimic DUMP Syndrome include lymphoid hyperplasia of the uvea; large–cell non–Hodgkin’s lymphoma; choroidal osteoma; diffuse choroidal hemangioma; uveal metastases; and uveal melanoma.

6. Clinical and Immunologic Characteristics of Melanoma–Associated Retinopathy (MAR) Syndrome

In the retinal degeneration associated with cutaneous melanoma—the MAR syndrome—patients frequently have an established diagnosis of cutaneous melanoma and develop vision problems years later, usually associated with non–ocular metastasis. In our series the latency from melanoma diagnosis to recognition of MAR syndrome averaged 3.6 years (range 2 month to 19 years).\textsuperscript{33,40,55,124–152} The earliest report of a patient with MAR–like syndrome is that reported by DuBois et al. in 1988, initially attributed night blindness to migraine.\textsuperscript{129} In 1991, the same authors reported the same case more than once, the exact number of reported cases is difficult to determine. We have serum samples from 25 MAR patients, collected from 1992 to 2000. Features of 14 of these cases have been previously documented; 11 cases are described here for the first time. In this report, we add the features of these 11 cases to the 51 cases previously reported.\textsuperscript{55} In our report of 62 MAR patients there were 33 men and 7 women (4.7 to 1 men over women). The age of onset was averaged 57.5 years (range 30 to 78 years). Visual acuity of 20/60 or better was initially present in 82% of the cases. Fundus examination was normal 44%, optic disc pallor 23% and retinal vessel attenuation was present 30%. Vitreous cells were present in 30%.\textsuperscript{55}

While in our series the fundus was usually normal except for optic pallor, several other investigators have reported a variety of fundus findings. Borkowski et al reported 2 patients, one patient with an oval shaped white lesion in the outer retina and patient 2 with well–circumscribed chorioretinal atrophic lesions, (note the fundus had been normal 4 years earlier). Patient 2 developed vitiligo with onset of the new metastases and the fundus lesions.

The seminal paper on MAR syndrome, by Berson and Lessell\textsuperscript{130}, postulated a paraneoplastic cause of night blindness in a patient with malignant melanoma. Subsequently, Milam et al recognized that patients with MAR have circulating IgG autoantibodies showing specific immunofluorescent staining of some human rod bipolar cells.
The bipolar cell antigens upon which these antibodies react remain unknown; some evidence suggests that they are made of polar lipid.\textsuperscript{125}

MAR syndrome affects predominantly males. The male-to-female ratio of 4.7:1 far exceeds the 5:4 incidence of malignant cutaneous melanoma in the United States.\textsuperscript{157} MAR patients have been believed to retain near-normal visual acuity, color vision and central visual field\textsuperscript{40}, but our review clearly shows that some lose central vision. Visual acuity may deteriorate later on, showing central and peripheral loss with progression.

Visual symptoms include shimmering, flickering, or pulsating photopsias and difficulty with night vision. The ERG shows the typical features of a markedly reduced dark-adapted b-wave, and preservation of a-wave, resembling that seen in CSNB.\textsuperscript{40} Defects in the function of cones “ON”-center bipolar cells and blue-sensitive cones occur in some patients.\textsuperscript{131-132, 136} There is evidence that the damage is restricted to cells of the magnocellular pathway.\textsuperscript{139} The “Off” or hyperpolarizing, bipolar cells are said to be spared.\textsuperscript{131, 136} Other abnormal electrophysiologic findings reported in some MAR patients are reduced a-wave amplitude in the photopic or scotopic ERG\textsuperscript{133, 143}, reduced amplitudes of the photopic ERG\textsuperscript{131, 133, 136-137}, reduced amplitudes of oscillatory potentials\textsuperscript{131-134}, maximum stimulus intensity amplitude reduction\textsuperscript{138}, abnormalities in the 30Hz-flicker response latency\textsuperscript{132-133, 138, 141} or amplitude\textsuperscript{133, 136}, and an abnormal pattern-ERG.\textsuperscript{145} Alexander reported in two patients with MAR that the contrast sensitivity loss is not specific to the magnocellular pathway, but related to the spatial frequency of the test target and consistent with the dysfunction of the bipolar cell layer.\textsuperscript{158} Kim et al reported a case of MAR Syndrome with spontaneous improvement of the rod system function.\textsuperscript{159}

In our study, two patients showed an almost extinguished ERG pattern with diffuse loss of both a-wave and b-wave. One patient had an abnormal ERG in only one eye.\textsuperscript{155}

The MAR syndrome is generally believed to occur only after patients have developed metastatic melanoma.\textsuperscript{125} Our review however, disclosed two patients who presented with MAR before the diagnosis of a primary melanoma, three who had no evidence of metastatic disease, five who presented with a simultaneous diagnosis of metastatic cutaneous melanoma and MAR, and six whose metastasis was diagnosed after the onset of MAR. In addition, one case of MAR-like syndrome has been described in a patient with antiretinal bipolar cell antibodies with no cutaneous melanoma after 4 years of follow up.\textsuperscript{160}

The immunologic and electrophysiologic abnormalities in patients with MAR syndrome suggest that the underlying pathogenic mechanism is molecular mimicry, such as has been described in other paraneoplastic syndromes.\textsuperscript{56} According to this mechanism, MAR syndrome occurs when susceptible individuals produce an immune response that cross-reacts with retinal rod bipolar cells, with which the melanoma cells share antigenic epitopes. Neuroretinal transmission from the photoreceptors through the inner retina is then disrupted.\textsuperscript{125, 132} Our finding that the metastatic melanoma removed from patient 58 expressed antigens that react with rabbit anti-whole bovine retina antibodies supports the proposal of molecular mimicry as the underlying pathogenic mechanism in MAR syndrome.

Immunologic heterogeneity is recognized in MAR. Involvement of “ON” bipolar cells has been implicated.\textsuperscript{125, 131, 142} We previously reported that one patient had an autoantibody reaction with a 22-kDa neuronal antigen found in the retina, but not in the optic nerve.\textsuperscript{161} Other studies have suggested that a novel membrane-associated 33-kDa protein and a 35-kDa retinal Muller cell protein could be the MAR antigens.\textsuperscript{134, 162} In our study, the variety of retinal antigens involved in indirect immunohistochemical staining and Western blot analysis strongly suggests that several antigens, shared by the retina and the neoplasm, may be involved. In addition, anti-bipolar cell antibodies have been demonstrated in a patient with CAR syndrome from adenocarcinoma of the colon.\textsuperscript{163} Transducin was demonstrated in a patient with MAR syndrome.\textsuperscript{164}

Although our patients’ sera specifically recognized retinal bipolar cells with indirect immunohistochemistry, we were unable to identify MAR-specific retinal antigens by Western blot technique. It has been postulated that the absence of specific staining by MAR sera on Western blots could be due to modification of amino groups by paraformaldehyde, denaturation by sodium dodecyl sulfate, and obscuration of MAR-specific antigen by a nonspecifically stained component.\textsuperscript{132} It is possible that the MAR-specific retinal antigens may not be proteins, but gangliosides, proteoglycans\textsuperscript{132}, lipids\textsuperscript{125}, carbohydrates, or a combination of these substances.

Brazhin et al they developed a murine model for MAR in ret-transgenic mice. They found arrestin and transducin in MAR patients. Adoptive transfer of splenocytes from tumor-bearing wild-type mice led to induction of retinopathy in 4/16 mice. This suggests that MAR can be mediated by humoral and/or cellular immune response against a number of CAR antigens which may function as paraneoplastic antigens in MAR.\textsuperscript{165} In addition they demonstrated for the first time to different autoantibodies against two different cancer related proteins in the same MAR patient. These antibodies were against arrestin and transducin.\textsuperscript{165-166} They feel that MAR syndrome is likely induced by an immune response against multiple retinal antigens\textsuperscript{166-167}.

Milam et al reported that sera from MAR patients and some normal subjects produced nonspecific background labeling of all parts of the human retina and specific staining of nerve fiber layer.\textsuperscript{132} A pattern of diffuse staining of human MAR IgG throughout the retina in rhesus monkey eyes was recently reported.\textsuperscript{142} We found that the analysis of MAR sera by indirect immunohistochemistry on sectioned rhesus monkey eyes disclosed diffuse antibody involvement with optic nerve, retinal nerve fiber layer and photoreceptors, as well as bipolar cells. Notably, over half of the UC Davis patients
showed optic disc pallor. The staining of nerve fiber layer, optic nerve and ganglion cells may be related to damaged neurotransmission or merely a harmless epiphenomenon. Recently other authors have found the melanoma-associated retinopathy may be related to a variety of anti-retinal antibodies, as we discussed in our article.55 Potter et al,164 found recognition of a transducin, a novel melanoma-associated retinopathy antigen which may be important when identified by Western blot. They found no immunoreactivity against bipolar cells by immunohistochemistry.

Ladewig reported on the screening of 77 serum samples with 51 patients with different stages (Am Joint Committee on Melanoma Cancer Stages I–IV). Of the 77 samples 53 (69%) were found to have antibodies reactive with various components of retina. Statistical analysis revealed a correlation between antibody activity and the stage of the disease with the higher percentage of antibody activity in advanced stages of melanoma. None of the patients had symptoms of MAR. Follow-up studies of these patients will be needed to see if any develop MAR and the significance of these findings.168 Pfohler has reported on the high frequency of subclinical findings of MAR in patients with melanoma.169 No follow-up to these 53 patients with antibodies reactive with various components of the retina has been published. However, I have had a personal communication with Claudia Phohler in October 2009 and she relates to me that of the 49 patients followed since their original papers168–169, only one patient developed MAR Syndrome. The MAR Syndrome resolved with treatment of the melanoma. None of the other 49 patients who had retinal antibodies developed MAR Syndrome. Pfohler has also reported that antiretinal antibodies are not always associated with prolonged survival in melanoma patients.270

Histopathologic studies of postmortem retinas from MAR patients have been previously reported.135, 140 In the first case, Okel et al135 found considerable loss of macular anatomy, with marked degeneration of photoreceptor cells and extensive destruction of the neurosensory retina beyond the bipolar layer. In the second case, Gittinger and Smith140 observed marked reduction in the density of bipolar neurons in the inner nuclear layer. Photoreceptor cell nuclei in the outer nuclear layer were normal. Ganglion cells were present, although many showed evidence of trans-synaptic atrophy. These anatomical changes are consistent with the clinical, immunologic and electrophysiologic data that implicate the bipolar cells as the primary site in MAR syndrome. By contrast, in one patient whose eyes were made available for our study, histopathologic examination revealed no apparent anatomical abnormalities by light microscopy, even though indirect immunohistochemistry showed strong antibody activity upon nerve fiber layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, outer segment of photoreceptor cells, and the retinal pigment epithelium.139 Thus, the 3 cases of histopathology discussed above (two previously reported cases and the current study) showed the diverse findings of normal retinal structure to widely destroyed retinal structure. New information has been reported by Bazhin about the histology in MAR.165 Bazhin et al demonstrated in their murine model for MAR in ret-transgenic mice that melanoma-bearing mice showed similar signs of retina degeneration as reported in some patients with MAR. Specifically they found degeneration of photoreceptors, bipolar cells and pigment epithelium. This suggests that not only proteins of bipolar cells, but also photoreceptor proteins and possibly proteins of pigment epithelium could function as paraneoplastic antigens in MAR.165

Recently Janaky171 identified what appeared to be a classic case of MAR Syndrome. The patient had classic MAR Syndrome in the right eye with typical ERG changes in field loss, while the left eye had normal vision and fields. It may be the first case report of a unilateral MAR Syndrome that after 18 months failed to spread to the second eye.

Treatment of the visual loss of MAR has often been ineffective. Occasionally combinations of cytoreductive surgery, x-irradiation, intravenous corticosteroids, plasma exchange, and IVIg have shown some benefit.55 Others have also found similar results with IVIG in case of MAR Syndrome.272

IVIg has been shown to be efficacious in the treatment of two of three patients with paraneoplastic visual loss associated with CAR Syndrome.173 It has been useful in other autoimmune neurologic diseases, including Guillain–Barre Syndrome, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, multiple sclerosis, dermatomyositis174–177, and in other immunologic ophthalmologic conditions, such as ocular cicatricial pemphigoid178, refractory uveitis179–180 eye.

All preparations of IVIg are comparable in safety, efficacy and cost. While the different pools of human donors used by the various manufacturers contain a wide range of anti-idiotypic antibody specificities there are no documented differences in the efficacy of certain products or lots for a given patient or a specific disease. The empirical therapeutic dose of IVIg is 2g/kg. While the past practice has been to divide the total dose for infusion into 5 daily doses of 400 mg/kg each, the current recommendation is to divide the total dose into 2 daily doses of 1g/kg each. The rate of infusion should not exceed 200 ml/h or 0.08 ml/kg/min. Because of the drug’s rapid diffusion to the extravascular space, achieving a high concentration of IVIg within 2 days may enhance its efficacy.174

There is concern that immunomodulatory therapy such as IVIg, while decreasing the titer of circulating autoantibodies, may increase the cancer mortality because MAR patients may have antibodies that are protective against tumor spread. However, in the patients whom we studied, there is no difference in survival between MAR patients, treated or untreated, and those without MAR. There are three experimental studies that show the efficacy of IVIg as an anti-tumor agent.181–183
Current research suggests that cytoreductive surgery (complete metastasectomy) and adjuvant immunotherapy should be the initial treatment for most patients with melanoma metastatic to distant sites, since 90% of such patients have only one to three metastatic sites detectable with modern scanning technologies. Adjuvant immunotherapy can be used after the induction of a complete clinical remission by cytoreductive surgery. In a recent case of CAR Syndrome secondary to adenocarcinoma of the colon with retinal anti–bipolar cell antibodies, the ERG and visual fields were markedly improved after such therapy. Thus, effective treatment of cancer may result in elimination of associated anti–retinal antibodies and improved retinal function.

Cancer cells, including those of malignant melanoma, generate factors that facilitate tumor growth by suppressing the immune system. The degree of general immunosuppression correlates with the total burden of melanoma cells in the body. Melanoma cells also express multiple melanoma–associated antigens that may induce the production of circulating autoantibodies or other factors that block the ability of lymphocytes to kill melanoma cells, or activate T cells to suppress the anti–tumor response. These autoantibodies may cross-react with retinal rod bipolar cells in susceptible hosts, resulting in MAR Syndrome. Therefore, by removing most of the immunogenic activities of melanoma cells and decreasing the tumor burden, cytoreductive surgery not only facilitates the resolution of MAR, but also allows the recovery of the host’s anti–tumor immune response.

In our series among the 7 MAR patients who experienced visual improvement, 4 had cytoreductive surgery. Two patients improved with cytoreductive surgery alone, and two others received cytoreductive surgery in addition to IVIg. The importance of decreasing melanoma tumor burden in treatment of MAR Syndrome is further demonstrated by one particular patient’s clinical course. This individual experienced a worsening of visual acuity every time the metastasis recurred and improvement in visual acuity when the metastatic disease was reduced with radiation therapy. In MAR, as well as other CNS paraneoplastic syndromes, other therapies have been generally less effective than cytoreductive surgery and IVIg.

Results of a randomized trial in the adjuvant treatment of metastatic malignant melanoma have shown promise. Patients receiving adjuvant immunotherapies such as CancerVax/BCG and GM2 ganglioside/BCG vaccine had prolonged disease–free intervals and increased survival rate compared to those who received BCG alone. Vaccination with treated autologous cells has been attempted. Dendritic cell–based vaccine and gene therapy have also been promising. Another emerging therapy involves the transfection of cutaneous malignant melanoma nodules with retrovirus–mediated herpes simplex type 1 thymidine kinase suicide genes, rendering the transfected cells susceptible to ganciclovir. In another study, autologous tumor cells transfected with IL–2 genes were injected back into patients to generate an immune response. Yet another approach involves injection of vaccinia/GM–CSF constructs directly into subcutaneous metastases.

The treatment of patients with malignant melanoma and MAR syndrome should be directed at decreasing the tumor burden, with resection of visible metastatic tumor masses by cytoreductive surgery so that any adjuvant immunotherapy can become more effective. Other medical treatments are reserved for patients whose ophthalmic manifestations are not relieved by these approaches.

7. Autoimmune–Related Retinopathy and Optic Neuropathy (ARRON) Syndrome
(Not Associated with Cancer)

Patients with autoimmune–related retinopathy and optic neuropathy (ARRON) syndromes may often go unrecognized, and may be more common than either CAR or MAR syndromes. Although definitions of ARRON syndrome may evolve to include additional forms of vision loss, our experience with this syndrome has led us to describe it as a diverse group of patients, without malignancy, who produce antibodies that are reactive with the optic nerve an/or retina; and who may be responsive to steroid treatment or other immunomodulators. Those patients who do not initially exhibit abnormal antibody activity may later do so as their vision loss progresses. It is also possible that patients may experience immunologic abnormalities that are not detected by the methods described in this report.

The term “autoimmune–related” is used rather than simply “autoimmune” because it is unclear whether, in all cases, the antibodies that are generated from the retina and optic nerve are part of the etiology of the visual loss, or whether they truly represent an epiphenomenon to non–specific breakdown of retinal and optic nerve proteins. We believe that many of these antibody reactions are related since immunologic treatment seems to help some of these patients. There are a variety of autoimmune reactions throughout the retina, choroid plexus, optic nerve, and blood vessels of the retina and optic nerve.

We have reported on a group of ARRON patients. We found the syndrome more commonly in women than men, the average age being 50. The visual loss was often asymmetric with visual acuity varying from 20/20 to no light perception. Eleven of 12 patients had optic neuropathy with ERG abnormalities present in 10 out of 11. Eight out of 12 patients had other systemic autoimmune diseases. Varieties of treatments have been tried with variable success and are generally based on standard therapy for other systemic diseases, which include: prednisone, IVMP, immunosuppressive therapy, plasma exchange and IVIg.

Historically, the first reports of autoimmune optic neuropathy by Rush et al, Dutton et al, Jabs et al, Kupersmith et al, Riedel et al, and Frohman et al described patients with steroid–responsive optic
neuropathy. These patients generally had an acute to subacute onset rather than the chronic course of visual loss that many of our ARRON patients have demonstrated. Rush et al\textsuperscript{218} reported on a patient with a positive ANA and benign monoclonal immunoglobulin G (IgG) band, who developed an optic neuropathy that was responsive to corticosteroids. Dutton et al\textsuperscript{219} described three patients with lupus–like syndromes and positive ANAS who presented with retrobulbar optic neuritis. Their vision improved with pulse IVMP acutely and was maintained with continued administration of prednisone and other immunosuppressives. The authors stress the importance of differentiating autoimmune optic neuropathy vs. multiple sclerosis. Patients with optic neuropathy of an autoimmune origin may become irreversibly blind if untreated, but patients with multiple sclerosis commonly recover spontaneously. They also bring attention to the early use of intensive steroid therapy, as they believe that is what led to good visual results in three of the four eyes in their study.

Jabs et al\textsuperscript{220} reported seven women with SLE who presented with optic neuropathy. The authors state the importance of considering the possibility of SLE in young women who present with unilateral or bilateral optic neuropathy. Corticosteroid therapy improved the vision in four of their seven patients. Kupersmith et al\textsuperscript{221} included a case series of 14 patients. Nine patients had bilateral optic neuropathy. Four patients started with a unilateral optic neuropathy, but involvement of the other eye developed from 1 to 17 years later. These patients lacked clinical signs of systemic collagen vascular disease, but they had blood abnormalities such as positive ANA (11 of 14 patients), or less consistently, positive Raji (1 of 3 patients evaluated) or anticardiolipin antibodies (4 of 5 patients evaluated). Skin biopsies in six of the seven patients evaluated showed IgG, IgA, IgM, or C3 deposits. The results of the treatment were remarkable. Eleven patients had dramatic improvement of vision with megadose intravenous corticosteroid therapy, nine of whom had previously failed to benefit from conventional doses of oral prednisone. Immunosuppressive therapy was later used to supplement corticosteroid therapy in maintaining vision. Their goal was to determine the lowest effective dose or to eventually eliminate corticosteroid entirely.

Riedel et al\textsuperscript{222} reported two cases of steroid–responsive optic neuropathy following periods of immunosuppressive therapy over the years. Both patients had C3 and IgM deposition perivascularly and at the dermo–epidermal junction on skin biopsy. The diagnosis of autoimmune optic neuropathy was made on the presence of the immune complex deposition. Both patients responded to IVMP followed by oral prednisone use. Both were slowly tapered off corticosteroids after stabilization of their vision.

Frohman et al\textsuperscript{223} reported a 12–year old patient with steroid–dependent optic neuropathy who experienced recurrent episodes of optic neuritis during multiple attempts at tapering the steroids. The patient’s serum was assayed and did not contain circulating antibodies against the optic nerve and retina. He was found to have a dysgammaglobulinemia, with decreased levels of IgG subclasses 2 and 3. Due to the long–term prednisone use, the patient experienced complications including growth delay and cushingoid features. However, with the initiation of a monthly regimen of IVIg, he was successfully tapered off the steroids without any complications or recurrence of visual symptoms.

These earlier reports by Rush et al\textsuperscript{218}, Dutton et al\textsuperscript{219}, Jabs et al\textsuperscript{220}, Kupersmith et al\textsuperscript{221}, Reidel et al\textsuperscript{222} and Frohman et al\textsuperscript{223} described patients with steroid–responsive optic neuropathy who probably had an autoimmune optic neuropathy. These early cases of steroid–responsive optic neuropathy may well have been cases we would now consider ARRON syndrome. However, available laboratory techniques at the time did not allow for detection of antibodies against the optic nerve and retina. Additionally, it is important to remember that antibodies may not always be detected secondary to immunosuppressive therapy or normal sampling serum variation. Alternatively, antibodies may be present but undetectable by current laboratory techniques. Multiple, serial antibody testing may be necessary to follow the course of a patient’s disease or response to treatment.

More recent reports that we would include in the ARRON syndrome include Mizener et al\textsuperscript{224}, Whitcup et al\textsuperscript{225}, Peek et al\textsuperscript{226}, and Keltner et al\textsuperscript{216}. These studies included patients with antibodies to various layers of the retina and optic nerve in the absence of cancer. Mizener et al\textsuperscript{224} described two patients with anti–retinal antibodies that reacted with the inner plexiform layer of the retina. Both patients had severe monococular visual loss with photopsias, ring scotomas, and abnormal ERGs despite normal appearing fundi. They both had family and personal history of autoimmune disease. The evaluation for cancer in these patients was negative. Similar to patients described by Mizener, the patients in this study also had asymmetrical visual loss. Although the two patients in Mizener et al.’s study\textsuperscript{224} both had photopsias, our group of ARRON patients seems to lack the photopsias (three out of our 12 patients experienced photopsias) that characterize CAR patients.

In Whitcup et al’s study\textsuperscript{221}, a patient with antibodies directed against recoverin produced strong labeling of the rods, cones, outer plexiform layer, and certain cone bipolar cells. Also, this patient had a strong cellular immune response against recoverin. Despite two years of extensive evaluation for malignancy, none was ever found. The authors suggested the term “recoverin–associated retinopathy” for their patient. Adding to this complexity, Peek et al\textsuperscript{226} found antibodies that were reactive with Muller cells in a patient with progressive loss of vision over four years without malignancy. ERGs of both eyes showed greatly reduced b–waves. Keltner et al\textsuperscript{216} described eight patients (only one with malignancy) who
displayed immunologic reactivity to a 22–kD antigen. A follow-up on case one of the studies is also presented in this report.

There are other reports of recoverin antibodies and other proteins found in retinal degeneration. Anti-recoverin immunoreactivity was found in 10 patients without malignancy from a sample pool of 521 patients with retinitis pigmentosa (RP). The authors conclude that there may be rare cases of CAR–like syndrome in the category of simplex RP and that these patients may also have anti-recoverin antibodies that could exacerbate their visual loss. However, Adamus points out in an editorial that these 10 patients had antibodies to multiple retinal proteins and that antibody titers were not measured to demonstrate the higher intensity or quantity of one antibody over others. The patients’ sera contained diffuse antibodies to retinal proteins; thus, it is difficult to assign a more important role to one protein than the others, but recoverin is a recognized potent autoantigen.

Although the presence of systemic autoimmune disease is not an inclusion criterion for ARRON syndrome, many of our patients have one or more systemic autoimmune disease. Those include patients with Lupus (a rare, but well documented, cause of optic neuropathy), celiac sprue, idiopathic thrombocytopenic purpura, rheumatoid arthritis, Sjogren’s syndrome, psoriasis, psoriatic arthritis and hypothyroidism. There has been reported a case of autoimmune retinopathy after chronic renal allograft rejection.

There is increasing evidence of autoimmunity in other retinal disorders such as the white spot syndromes (WSS) (i.e. multifocal choroiditis/punctate inner choroidopathy (MFC/PIC), acute zonal occult outer retinopathy (AZOOR), bird shot chorioretinopathy, multiple evanescent white dot syndrome, serpiginous choroiditis, acute posterior multifocal placoid pigment epitheliopathy (APMPPPE), acute macular neuroretinopathy, and relentless placoid chorioretinitis). Pearlman et al reported that there was an increased prevalence of systemic autoimmunity in both patients with WSS and their first and second-degree relatives. The authors suggest that WSS occur in families with inherited immune dysregulation that predisposes to autoimmunity.

ARRON patients may have a lifetime of dealing with numerous, recurring health–related issues. We previously reported a 22–kD patient who was free of antibodies for 11 years while under immunosuppressive therapy. Although she recently developed recurrence of her immunologic ocular hypersensitivity to a new 45–kD reaction on Western blot and to outer segment photoreceptors on IFA, she does not appear to have cancer or further progressive visual loss. She remains under close surveillance for any visual changes.

Recently Ferreya reported a retrospective study of 30 patients with AIR with 11 of these nonparaneoplastic patients having cystoid macular edema (np/AIR/CME). The CME they reported showed on OCT demonstrated intraretinal cystic spaces or schisislike spaces, many of these case do not have leakage on fluorescein angiography, and they believe that patients with AIR macular changes re a form of degenerative schisis. Heckenlively has reported in prospective masked studies that 90% of patients with RP and cysts have circulating antiretinal antibodies by means of Western blot analysis compared with 13% of patients with RP without macular cysts and 6% of controls. They also reported the personal autoimmune history of this cohort and the prevalence of autoimmune disease was 40% (12 of 30 patients). The breakdown of the personal autoimmune history was 6 of 13 (46%) in the nonparaneoplastic AIR (npAIR) group, 4 of 11 (36%) in the npAIR/CME, and 2 of 6 (33%) in the CAR group. We have reported similar phenomena in our ARRON patients. However, Ferreya did not report on the incidence of optic nerve antibodies in the patients. We like to use the term ARRON with CME for those AIR Patients who had CME and ARRON for those AIR patients without CME. The reason is stated above is that it is unclear if the antibodies generated from the retina and optic nerve are part of the etiology of the visual loss, or whether they truly represent an epiphenomenon to non–specific breakdown of retinal and optic nerve proteins. In this paper Ferreya reports that 21 out 2010 Annual Meeting Syllabus | 279
important aspect of treating patients with ARRON syndrome is to be certain that they have progressive visual loss and no evidence of cancer. We have seen several patients with antibody reactions to the retina or optic nerve, but who appear to have visual loss that is stable; thus, the inciting factor appears to have been removed or is no longer a problem. Since these immunologic treatments are not benign and are also rather costly, it is essential to be sure that there is objective evidence of visual function loss before proceeding with treatment. The patient should also understand that there may not be a return of visual function, and that the goal of treatment may only be the prevention of further visual loss.

We have recently reported on a case of ARRON syndrome treated with autologous nonmyeloablative hematopoietic stem cell transplantation (HSCT) in a 47 year old woman with progressive visual and bearing loss. Clinical manifestations appeared to stabilize and may suggest that autologous HSCT may have a role in the treatment of ARRON syndrome.\(^1\)

In summary, autoimmune–related retinopathy and optic neuropathy (ARRON) syndrome is probably much more common than has been previously recognized. Patients who are suspected of having autoimmune–related retinopathy and optic neuropathy should be evaluated first for the presence of cancer and given an ERG. If no cancer is found and appropriate immunologic testing demonstrates that the patient has antibodies to the retina or optic nerve, they may have ARRON syndrome. Appropriate treatment may be necessary if patients show evidence of progressive visual loss. However, since all patients may not respond to steroid use, other immunomodulators may be necessary to slow or halt the deterioration of vision.

**CME ANSWERS**
1. E
2. C
3. E

**REFERENCES**


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