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MAJOR REVIEW

Paraneoplastic Retinopathies and Optic Neuropathies

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Abstract. Unusual neuro-ophthalmologic symptoms and signs that go unexplained should warrant a thorough investigation for paraneoplastic syndromes. Although these syndromes are rare, these clinical manifestations can herald an unsuspected, underlying malignancy that could be treated early and aggressively. This point underscores the importance of distinguishing and understanding the various, sometimes subtle, presentations of ocular paraneoplastic syndromes. Outlined in this review article are diagnostic features useful in differentiating cancer-associated retinopathy, melanoma-associated retinopathy, and paraneoplastic optic neuropathy. These must also be distinguished from non–cancer-related eye disorders that may clinically resemble cancer-associated retinopathy. The associated antibodies and histopathology of each syndrome are presented to help in the understanding of these autoimmune phenomena. Treatment outcomes from reported cases are summarized, and some potential novel immunotherapies are also discussed. (**Surv Ophthalmol 48:**12–38, 2003. © 2003 by Elsevier Science Inc. All rights reserved.)

Key words. autoimmune • cancer-associated retinopathy • melanocytic-associated retinopathy • optic neuropathy • paraneoplastic

I. Cancer-Associated Retinopathy

Cancer-associated retinopathy (CAR) has been thought to be one of the most common paraneoplastic retinopathies. Its incidence is equal among women and men. At least 55 cases have been reported in the literature so far (Table 1). Although the CAR syndrome is believed to be more common that the melanoma-associated retinopathy (MAR) syndrome, review of the current literature shows more documented cases of MAR than CAR. A possible explanation for this unexpected increased frequency of MAR relative to CAR could be related to a greater decrease in the incidence of invasive lung cancer compared to invasive skin melanomas in men and women in the past 30 years in the United States. According to the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review, the annual percent change (based on rates age-adjusted to the 2000 U.S. standard population) for invasive lung and bronchial cancer decreased from 3.0 to −0.9 from 1973 to 1999. During the same time period trends in the SEER incidence for invasive skin melanomas showed less of a decline from 6.1 to 2.8 annual percent change.[113] Further epidemiologic studies will be needed to confirm this hypothesis.

Any adult with unexplained visual loss, with rod or cone dysfunction, or with known or suspected malignancy in the absence of other neurologic symptoms should undergo a thorough investigation for CAR.[57]

Symptoms usually present bilaterally, and rarely sequentially, over a period of several weeks or months before the underlying malignancy is diagnosed. Small-cell lung cancer is most commonly associated with CAR.[5,19,22,41,43,44,45,55,60,62,69,78,89,96,101,103,108,115,120,123,126,128,129,131]

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TABLE 1

Frequency of Malignancies Associated with Cancer-Associated Retinopathy

Types of Malignancies Associated with CAR	Number of Reported Cases in the Current Literature
Lung[5,19,22,41,44,45,55,60,62,69,78,89,96,101,103,108,115,119,120,123,126,128,129,131]	38
Endometrial[3,34,120,122,129]	5
Cervical[45,129]	2
Breast[21,75,117,122]	3
Ovarian[47,139]	2
Lymphoma[66]	1
Colon[58]	1
Pancreatic[45]	1
Prostate[90]	1
Bladder[90]	1
Laryngeal[90]	1
Metastases of unknown primary[90]	1

Gynecologic[3,30,34,45,47,66,100,122,126,129,139] and breast cancers[21,75,122] are the second most common malignancies and less commonly, non-small-cell lung cancer,[119] pancreatic cancer,[45] lymphoma,[66] prostate, bladder, and laryngeal cancers.[90] Most recently, colon cancer has been found to be associated with CAR (Table 1).[58] Patients may experience transient monocular dimming or loss of vision in both eyes at the onset, and even transient entoptic symptoms, such as flickering lights. They may even report that their vision is better if they wear dark sunglasses.[57]

CAR affects both cones and rods. Photosensitivity and prolonged glare following light exposure, reduced visual acuity, decreased color perception, and central scotomas are all features of cone dysfunction. Whereas rod dysfunction is represented as nyctalopia, prolonged dark adaptation, midperipheral (ring) scotomas, and more extensive peripheral visual field deficits. CAR is a subacute, progressive autoimmune retinopathy in which the patient will ultimately lose vision in both eyes.[94]

Although the retina may appear normal early in CAR, attenuated arterioles, thinned and mottled retinal pigment epithelium, and minimally pale optic disks usually appear within several months.[94] Vitreous cells, arteriolar sheathing, and periphlebitis suggestive of inflammation can also be seen later.[7]

Sawyer et al[120] were the first to correlate the histopathologic processes underlying these clinical changes in three postmenopausal women, of which two had small-cell lung carcinoma and one had metastatic oat-cell lung carcinoma. Diffuse photoreceptor degeneration of both cones and rods are present with or without any inflammation (Fig. 1). Scattered melanophages in the outer retina can also occasionally be seen. Ganglion cells in the inner retina, the optic nerve, and the geniculocalcarine pathway are all spared.[22,120]

Cross reactivity between cancerous and retinal proteins is responsible for initiating the immune-mediated cascade of events that ultimately leads to photoreceptor degeneration, thus participating in the pathogenesis of CAR.[7,25,44,66,129] Polans et al[108] demonstrated that recoverin, initially isolated and cloned by Thirkill et al,[130] was expressed in small-cell lung cancer cells in a patient with CAR who had circulating anti-recoverin antibodies. CAR is a heterogeneous group of autoimmune processes associated with several antigens expressed by rods, cones, or retinal ganglion cells. One of these antibodies first characterized by Thirkill et al[130] is directed against a specific photoreceptor protein, the 23-kDa retinal CAR antigen that has 90% homology with the amino acid sequence of bovine recoverin. It is the most common antigen associated with CAR.[127] The human gene for recoverin has been localized to chromosome 17.[92] A single mutation inactivating a copy of p53 tumor suppression gene could possibly lead

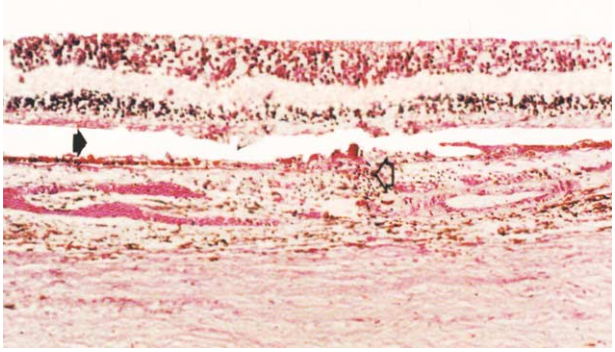

Fig. 1. Hematoxylin-eosin-stained sections through the retina revealed loss of the retinal outer nuclear and photoreceptor layers (black solid arrow) with inflammatory cells (open arrow) in a patient with cancer-associated retinopathy associated with small cell lung carcinoma (original magnification × 50).

to an increase of recoverin expression outside of the eye. The circulating antibodies would also be directed against retinal recoverin. This inactivated form of retinal recoverin could then cause closure of ion channels, depolarization of cells, and photoreceptor cell death.[7] Adamus et al[6,7] demonstrated that antirecoverin antibodies lead to apoptotic photoreceptor cell death in the CAR syndrome. As early as 24 hours, anti-recoverin Ab mediates DNA fragmentation and nuclear condensation in photoreceptor and bipolar cells in vivo.[6,7] In vitro and intravitreal injection of antibodies showed that anti-recoverin autoantibodies of patients with CAR could penetrate into living retinal cells, become localized inside the cell, and trigger cell death through apoptosis.[6,7] This antibody-mediated destruction of retinal cells was independent of complement. It has been proposed that the calcium-binding properties of recoverin could be involved in the process of penetration into retinal cells.[6] Recoverin is a calcium-binding protein located within retinal photoreceptor cells and bipolar cells.[6,7] It has been shown that the conformational changes induced by bound calcium enhances the binding of antibodies to recoverin.[107] The calcium-bound form of recoverin activates and regulates the enzyme that phosphorylates rhodopsin.[2,63] Blocking recoverin could, therefore, cause an increase in free calcium and lead to the activation of a nuclear endonuclease, a calcium-sensitive molecule, resulting in DNA fragmentation and nuclear condensation.[37,91,99,138] In vitro evidence from a study done by Maeda et al[86] in 2001 suggests that anti-recoverin antibody is incorporated into rod photoreceptor cells and modulates rhodopsin phosphorylation, which then leads to activation of caspase-dependent apoptotic pathways. Other evidence also exists to support the idea of antibodies triggering calcium-mediated apoptotic cell death in specific neurons. It has been shown that immunoglobulins could trigger calcium entry through neuronal calcium channels to result in the motor neuron cell death of patients with amyotrophic lateral sclerosis without any evidence of an inflammatory response.[11]

In addition to recoverin, other antibodies reactive against retinal antigens with different molecular weights have been found in patients with CAR. The second most common autoimmune retinal antibody is a 46-kDa protein[68] followed by a 45-kDa[139] and a 60-kDa[68] protein. Antibodies against 65-kDa heat shock cognate protein 70 (hsc 70) have also been identified in some patients with CAR.[99] The hsc 70 family of proteins are synthesized in response to various cellular stresses and present in normal unstressed cells. They play a role as chaperons, to help proteins translocate into organelles and to aggregate and degrade proteins. Elevated levels of heat-shock proteins in peripheral monocytes and serum autoantibodies against heat-shock proteins have been identified in patients with autoimmune diseases, such as lupus and rheumatoid arthritis. It is unclear how autoimmune reactions involving these various antibodies affect the onset and course of CAR, and what relationship exists between recoverin and hsc 70 in its pathogenesis.[98]

Anti-enolase antibodies (46-kDa) play a role in mediating retinal degeneration in CAR.[4] Alpha-enolase is a ubiquitous glycolytic enzyme (2-phospho-D-glycerate hydrolase) existing in three heterodimeric forms: alpha (non-neuronal enolase), beta, and gamma (neuronal-specific enolase). Enolase is a product of several types of tumors and enolase enzymatic activity has been detected in sera of some cancer patients.[9,24,56] In addition to its enzymatic activity, enolase may play a role in promoting cell survival. It has been suggested that neuron-specific enolase is associated with *c-myc* oncogene involved in the control of cell proliferation. Neuron-non-specific enolase may also serve to promote endothelial cell survival in hypoxia. The hypoxia-associated protein (HAP47) shares a significant homology with alpha-enolase.[1] The blocking of this yet unknown function of this protein by anti-enolase antibodies could reduce cell survival. Anti-enolase antibodies are further involved in immune-mediated cytotoxicity, leading to apoptosis in neuronal cells. It has been shown that this apoptotic effect depends on the presence of the antigen rather than the cell type, and the efficacy of the antibody could be related to the concentration of enolase in the cell.[1] Therefore, this evidence supports that anti-enolase-alpha may be potentially pathogenic to the retina.

In contrast to anti-recoverin antibodies directed against the outer segment of photoreceptor cells, antibodies to TULP-1 (tubby-like protein 1) protein are directed against the *inner* segment of these cells.[72] TULP-1 protein is localized in the *inner* segment from the myoid to the synaptic terminal regions of the outer plexiform layer in both rods and cones. The dominant autoepitopes are restricted to 18 amino acid residues at the N-terminus of TULP-1. This amino acid sequence of TULP1 has no homology with the calcium-binding site determinants of recoverin that react to the sera of CAR patients.[72] The anti-TULP-1 protein has been identified in a CAR patient with endometrial cancer.[72] Because TULP-1 is also one of the candidate genes for autosomal recessive retinitis pigmentosa, the TULP-1 antibodies may cause retinal degeneration in a similar mechanism to that in retinitis pigmentosa.[72]

More recently, antibodies against the photoreceptor cell-specific nuclear receptor (PNR) gene product has been identified in a 72-year-old woman with paraneoplastic retinopathy and lung cancer. The PNR

gene product is a nuclear receptor, a ligand-dependent transcription factor that mediates a wide variety of physiologic and regulatory processes.[35,53] Kobayashi et al[76] reported that the PNR gene was expressed in the outer nuclear layer whereas Chen et al[26] found expression in the inner nuclear layer and retinal pigment epithelium. PNR could be involved in suppressing genes whose expression is refractory to photoreceptor function.[8,76] PNR mutations play a role in retinal degenerations. PNR mutations have been found in patients with enhanced S-cone syndrome (ESCS) who develop enhanced sensitivity to blue light because of increased numbers of S cones and eventually progress to retinal degeneration.[46,61,88] These data suggest that anti-PNR antibodies interfere with PNR function by blockade of ligand binding leading to retinal degeneration. The anti-PNR antibodies in paraneoplastic retinopathies could have resulted from an immunologic reaction triggered by the tumor. The exact mechanism of how tumor breaks immune tolerance for retinal or neuronal proteins is still unkown.[33]

Other antibodies identified in patients with CAR and small-cell lung cancer have also been found to react against neurofilaments and retinal ganglion cells.[77]

The diagnosis of CAR requires the demonstration of anti-recoverin antibody in the serum, but its presence has recently been shown not to be specific for CAR, as will be explained later in the section on non-paraneoplastic autoimmune retinopathies. The electroretinogram usually reveals a markedly attenuated or absent photopic and scotopic response.[90] Cerebrospinal fluid reveals a nonspecific finding of a mild lymphocytic pleocytosis and an increased concentration of protein. If there is no family history of retinitis pigmentosa or similar disease, then such patients should also undergo a CT of the chest and a CT of the pelvis for lung, breast, and gynecologic cancers.[94]

Various immunotherapies have resulted in mild to moderate visual recovery. Steroids can transiently improve some vision if started before severe visual loss. Keltner et al reported the first case of steroid-responsive CAR.[66] Klingele et al then showed that prednisone given postoperatively at a dose of 60 mg qd could arrest the visual deterioration of CAR in a 43-year old woman with breast cancer.[75] Yoon et al[139] treated a 35-year-old woman with ovarian cancer-related CAR syndrome with systemic steroids and chemotherapy directed at the ovarian cancer. Although her vision temporarily stabilized, she eventually experienced photoreceptor degeneration, suggesting that once cell death has occurred, therapy is no longer of any benefit.[139] Keltner et al[69] demonstrated that although prednisone reduced CAR-related antibody titers to normal levels, visual function could only be stabilized. Monitoring antibody responses to retinal antigens therefore appeared to be useful in the decision whether to initiate prednisone therapy. He concluded that the increasing antibody titers to the CAR antigen probably occurs before progressive visual field loss and may be used as an indication for steroid therapy.[69]

Based on the reported cases of CAR in the current literature, treatment with steroids, especially with high-dose intravenous methylprednisolone more so than oral prednisone, have resulted in mild to moderate transient improvement in visual acuity and visual fields (Table 2),[5,19,30,41,60,62,66,69,75,89,90,100,101,103,115,123,129,139] or even no improvement.[30,96,119,120,122,123,139] Surgery, chemotherapy, and radiation therapy to treat the primary tumor did not alter the visual prognosis (Table 2).[21,34,45,55,66,78,90,115,131] Progressive worsening of vision despite removal of tumor cells suggests that the circulating antibodies persist to support ongoing inflammation that could eventually end in apoptosis. Prednisone and plasmapheresis together improved vision in one patient.[97] Plasmapheresis alone did not prevent progression of visual loss (Table 2).[126] In one study by Guy and Aptsiauri,[45] three patients with CAR were treated with IvIg. One patient had improvement in both visual acuity and visual fields; one had improvement in only visual field defects; and the other had only stabilization of vision (Table 2). In all of the above reported cases the very limited lifespan of the patients precluded observation of any long-term effects of treatment on visual function.

Potential therapeutic interventions for CAR have only recently been investigated. Chen et al[27] in 2001 demonstrated in vitro that elevated extracellular potassium levels could inhibit anti-recoverin IgG-mediated death of photoreceptors. The neuroprotective effects of elevated extracellular postassium was time- and dose-dependent. Their study suggests that mobilization of intracellular calcium protects cells by interfering with apoptotic signal transduction pathways. Therefore, therapeutic agents that mobilize intracellular calcium may potentially be able to prevent photoreceptor cell death in CAR.[27] Another potential immunotherapeutic approach involves the peripheral activation of recoverin-specific antitumor cytotoxic T-lymphocytes by injecting recoverin-derived HLA (human leukocyte antigen)-A24 binding peptides. Future design of immunotherapy based upon this mechanism could improve the prognosis of patients with CAR.[85]

II. Cancer-Associated Cone Dysfunction

Cancer-associated cone dysfunction is a subset of CAR syndrome. Only three cases have been reported so far in the literature (Table 3). Only cones are af-

TABLE 2

A Review of Treatment Outcomes for 55 Cases of Cancer-Associated Retinopathies (CAR) From the Current Literature

Authors and Year of Reference	Patient Age (yrs.)/Sex	Type of Cancer	Retinal Ag	Initial VA and/or VF	Type of treatment	Outcome of Treatment on VA and/or VF
Sawyer et al, 1976[120]	76/F		*	20/60 OD 20/30 OS	None	20/200 OD 20/120 OS
Patient 1		Anaplastic small cell lung cancer		Small central island of vision OD Ring scotoma with peripheral nasal defect OS		Small central island of vision OU
Patient 2	65/F	Small cell lung cancer	*	20/25 OU Inferior defect OD open nasally OS and bilateral ring scotomas at 15 degrees	Prednisone 100 mg/day	LP OU Preserved ring of vision at 40 degrees OD and temporally spared islands of vision OS
Patient 3	62/F	Endometrial sarcoma	*	20/40 OD 20/200 OS VF*	None	20/70 OD 20/HM OS
Kornguth et al, 1982[78]	72/M	Anaplastic small cell lung cancer with metastases	*	20/70 OD HM OS	Total brain XRT Cyclophosphamide, CCNU, methotrexate	LP OD NLP OS
Keltner et al, 1983[66]	61/F	Histiocytic lymphoma	*	20/25 OD 20/30 OS Ring scotomas OU	Prednisone 40 mg/day	20/25 OD 20/30 OS Improved VF
					Prednisone 80 mg/day with taper to 20 mg/day	20/25 OD 20/200 OS
					Cyclophosphamide, doxycycline, vincristine, high-dose prednisone, XRT	20/60 OU Peripheral field constriction OU
					Prednisone 80 mg/day with taper to 20 mg/day	NLP OU
Buchanan et al, 1984[22]	66/M	Small cell lung cancer	*	20/15 OD 20/15 OS Marked concentric constriction to 2 degrees OD and to 3 degrees OS Small central islands of vision	None	20/60 OU Stable VF

(*continued*)

TABLE 2

Continued

Authors and Year of Reference	Patient Age (yrs.)/Sex	Type of Cancer	Retinal Ag	Initial VA and/or VF	Type of treatment	Outcome of Treatment on VA and/or VF
Klingele et al, 1984[75]	43/F	Breast adenocarcinoma	*	HM OD 20/100 OS Dense central scotomas OU and marked peripheral constriction OD	Topical 1% prednisolone acetate OU and 5% homatropine hydrobromide OU, and 0.5% timolol maleate OU Prednisone 60 mg/day	HM OU CF OU Mild peripheral constriction with central scotomas OU
Grunwaldet al, 1987[44]	68/M	Small cell lung cancer	*	20/50 OD 20/20 OS Inferior arcuate defects OU and superior arcuate defect OS	Cyclophosphamide, doxorubicin, and vincristine	20/80 OD 20/30 OS
Thirkill et al, 1987[129]						
Patient 1	61/F	Undifferentiated cervical cancer	*	Poor VA OU Ring scotomas OU	Steroids	Improved vision
Patient 2	71/M	Non-small cell lung cancer	*	CF OU Small island of vision inferiorly OU	None	Progressive visual loss until totally blind over 7 months
Patient 3	64/M	Small cell lung cancer	*	HM OD 20/20 OS Overall depression of VF with central defect OS	None	NLP OU
Patient 4	68/M	Small cell lung cancer	*	*	None	*
Van der Pol et al, 1987[131]	37/M	Oat cell lung carcinoma	*	1.0 OU Central sparing to 10 degrees OD and normal VF OS ERG flat	Surgical resection of tumor, chemotherapy, XRT	Stable VF OD Concentric peripheral constriction and dense scotomas OS

(*continued*)

TABLE 2

Continued

Authors and Year of Reference	Patient Age (yrs.)/Sex	Type of Cancer	Retinal Ag	Initial VA and/or VF	Type of treatment	Outcome of Treatment on VA and/or VF
Crofts et al, 1988[30]	64/F	Undifferentiated endometrial cancer	50 kDa	20/400 OD 20/30 OS Ring scotoma OD and central sparing with residual VF islands OS	Prednisone 80 mg/day	No improvement
Thirkill et al, 1989[126]	60/F	Small cell lung cancer	*	20/50 OD 20/100 OS VF*	Plasmapheresis	No improvement
Jacobsen et al, 1990[60]						
Patient 1	71/M	Small cell lung cancer	23 kDa	20/200 OD 20/50 OS Central and midperipheral ring scotoma OD and midperipheral ring scotoma OS	Prednisone 60 mg/day, cytoxan, doxorubicin, and vincristine	20/200 OD 20/25 OS one year later Improved VF
Patient 2	67/M	Small cell lung cancer	*	20/80 OD 20/400 OS	Prednisone 80 mg/day	20/80 OD 20/200 OS
					Prednisone 60 mg/day	20/40 OD 20/200 OS
Gehrs et al, 1992[41]	69/M	Squamous cell lung cancer	*	20/30 OU	Surgical resection of tumor XRT	20/80 OD 20/60 OS
					Prednisone	Stable vision
Keltner et al, 1992[69]	68/M	Small cell lung cancer	*	20/25 OD 20/40 OS Generalized peripheral constriction and altitudinal defect	Prednisone 100 mg/day Prednisone tapered to 60 mg/day	20/25 OD CF at 1 OS 20/30 OD 20/50 OS
				OD and generalized constriction with multiple paracentral scotomas and central scotoma sparing macula OS	Prednisone 100 mg/day	20/30 OD HM OS
					Prednisone 20 mg/day	20/25 OD CF OS
Matsui et al, 1992[90]	68/F		*	20/50 OD	Surgical resection of tumors	*
Patient 1		Prostate, bladder, and laryngeal cancers		20/70 OS Peripheral constriction OU ERG flat VEP flat		

(*continued*)

TABLE 2

(Continued)

Authors and Year of Reference	Patient Age (yrs.)/Sex	Type of Cancer	Retinal Ag	Initial VA and/or VF	Type of treatment	Outcome of Treatment on VA and/or VF
Patient 2	67/F	Metastases of unknown origin	*	HM OU Irregular cecocentral scotomas OU ERG flat	Solumedrol Chemotherapy	Stable vision 20/40 OD 20/200 OS
Rizzo et al, 1992[115]						
Patient 1	59/M	Undifferentiated small cell lung cancer	48 kDa	20/20 OD 20/25 OS	Prednisone 80 mg/day XRT, adriamycin, cytoxan, cisplatin, VP-16, etoposide, and prednisone	20/20 OU Stable vision
Patient 2	67/M	Small cell lung cancer	*	20/80 OD 20/200 OS	Prednisone 80 mg/day	20/25 OU
Adamus et al, 1993[5]	64/F	Small cell lung cancer	23 kDa	20/50 OU Marked constriction with 4 separate islands of vision in periophery and in central 5 degrees OD and an island of vision within 5 degrees OS	None	NLP OU
Ohnishi et al, 1993[1023]	50/M	Small cell lung cancer	24 kDa 48 kDa	1.0 OD 0.6 OS Ring scotomas OU	Prednisone Solumedrol	0.7 OD 0.6 OS Mildly improved vision
Oohira et al, 1993[10]	62/M	Lung adenocarcinoma	*	0.8 OD 0.2 OS Blind spot enlargement OD and peripheral constriction OS	Prednisone 60 mg/day Prednisone taper to 30 mg/day Prednisone 30 mg qod	0.3 OU VF full to counting fingers 0.2 OU VF full to counting fingers Stable vision
Thirkill et al, 1993[128]						
Patient 1	72/F	Small cell lung cancer	*	*	None	*
Patient 2	56/M	Small cell lung cancer	*	20/200 OD 20/20 OS	None	*
Patient 3	67/M	Small cell lung cancer	*	20/40 OD CF OS	None	*

(*continued*)

TABLE 2
Continued

Authors and Year of Reference	Patient Age (yrs.)/Sex	Type of Cancer	Retinal Ag	Initial VA and/or VF	Type of Treatment	Outcome of Treatment on VA VF
Patient 4	75/M	Small cell lung cancer	*	20/40 OD LP OS	None	*
Patient 5	49/M	Small cell lung cancer	*	HM OD 20/60 OS	None	*
Patient 6	75/M	Small cell lung cancer	*	20/50 OU	None	*
Patient 7	67/M	Small cell lung cancer	*	20/40 OD CF OS	None	*
Patient 8	75/M	Small cell lung cancer	*	20/40 OD LP OS	None	*
Patient 9	49/M	Small cell lung cancer	*	HM OD 20/60 OS	None	*
Patient 10	75/M	Small cell lung cancer	*	20/50 OU	None	*
Eltabbakh et al, 1995[34]	65/F	Uterine sarcoma	23 kDa	20/40 OU Marked peripheral field restriction	Surgical resection of tumor, carboplatin, cyclophosphamide, and prednisone 60 mg/day	20/20 OD 20/25 OS Inferior nasal restriction OD Superior nasal and inferior temporal constriction OS
Polans et al, 1995[109]	62/M	Small cell lung cancer	23 kDa	Sudden vision loss OU ERG flat	*	*
Ing et al, 1996[55]	58/M	Small cell lung cancer	35 kDa, 40 kDa	20/30 acutely progressing to CF OD CF at 6, OS Marked constriction OU	XRT, cisplatin, etoposide, methylprednisolone, and methotrexate	LP OU
Suzuki et al, 1996[123]	63/F	Small cell lung cancer	*	20/25 OD 20/30 OS Marked peripheral constriction OU	Prednisone 25 mg/day	LP OU
Boucher et al, 1997[19]	58 M	Small cell lung cancer	23 kDa	6 OU Peripheral constriction with enlarged blind spots OU	Prednisone Prednisone taper	Stable VA Improved VF Constricted VF OU
Brink et al, 1997[21]	67/F	30 year history of breast cancer	*	20/30 OU	XRT	VA HM OU
Murphy et al, 1997[96]	74/M	Small cell lung cancer	*	CF OD 20/40 OS	Prednisone 100 mg/day and plasmapheresis	20/200 OD 20/25 OS
Adamus et al, 1998[3]	61/F	Endometrical cancer	Recovering (23 kDa) in serum and expression in endometrial cancer cells	20/70 CF Normal VF	Methylprednisolone	20/25 OD 20/400 OS Normal VF OD and paracentral scotoma OS
					Higher dose of methylprednisolone	Stable vision 23 kDa antigen negative

(*continued*)

TABLE 2

Continued

Authors and Year of Reference	Patient Age (yrs.)/Sex	Type of Cancer	Retinal Ag	Initial VA and/or VF	Type of Treatment	Outcome of Treatment on VA/or VF
					Plasmapheresis	Color vision immediately improved but worsened 1 month later ERG response decreased by 50% Antirecoverin antibody titers increased 3 months later Stable vision at HM OU one year later Antirecoverin antibody titers normal
					Tolpa Torf preparation (a natural immunomodulatory drug)	
Salgia et al, 1998[119]	72/F	Non-small cell lung cancer	23 kDa	6/200 OD 3/200 OS Paracentral defect from center of fixation to superotemporal region OS>OD	Prednisone 60 mg/day, XRT, cisplatin, and etoposide	No improvement
Guy et al, 1999[45]						
Patient 1	62/F	Small cell lung cancer	46 kDa	HM OU ERG attenuated	Surgical resection of tumor then IVIg 0.4 g/kg/day × 5 days	20/50 OD 20/40 OS Superior scotoma adjacent to blind spot OD and normal VF OS
Patient 2	77/F	Cervical cancer	23 kDa	LP OU ERG flat OU	Prednisone 80 mg/day and IVIg 0.4 g/kg/day × 5 days	No improvement
Patient 3	71/M	Pancreatic cancer	46 kDa	20/400 OD 20/20 OS Normal VF OD and arcuate and nasal defects OS	IV Solumedrol 1 g/day × 3 days then prednisone 60 mg taper	20/400 OD 20/20 OS
					IVIg 0.4 g/kg/day × 1 day	Improved VF OD Stable VF OS
Harmon et al, 1999[47]	75/F	Epithelial ovarian cancer	23 kDa, 45 kDa	Acute visual loss Od Generalized constriction OD then OS	Surgery, cyclophosphamide, and paclitaxel	*

(*continued*)

TABLE 2
(Continued)

Authors and Year of Reference	Patient Age (yrs.)/Sex	Type of Cancer	Retinal Ag	Initial VA and/or VF	Type of Treatment	Outcome of Treatment on VA and/or VF
Kashiwabara et al, 1999[62]	70/F	Small cell lung cancer	23 kDa	0.2 OD 0.1 OS VF*	IV methylprednisolone 1 g × days then prednisolone 40 mg tapered to 5 mg/wk; carboplatin, etoposide	Transient visual improvement HM OU
Masaoka et al, 1999[89]	69/M	Small cell lung cancer	23 kDa 70 kDa	0.5 OD 0.6 OS Paracentral scotomas OU	Solumedrol	0.6 OD 0.3 OS
					Cisplatin, etoposide, XRT	0.2 OD CF OS Enlarged paracentral scotomas OU
Yoon et al, 1999[139]	35/F	Ovarian cancer	45 kDa	20/25 OD 20/30 OS VF*	Prednisolone	20/100 OD 20/80 OS progressing to movement perception
Sobottka et al, 2000[122]						
Patient 1	68/F	Undifferentiated uterine cancer	23 kDa	HM OU Peripheral constriction OU	Prednisolone 100 mg/day	No improvement
Patient 2	58/F	Breast cancer	23 kDa	0.8 OU Peripheral constriction OU	Prednisolone 100 mg/day	No improvement
Eichen et al, 2001[33]	72/F	Poorly differentiated lung carcinoma	PNR	20/40 OD 20/30 OS Peripheral constriction OU	*	*

*Indicates information not available.

F = female; M = male; Ag = antigen; kDa =kilodaltons; VA = visual acuity; VF = visual fields; CF = counting fingers; HM = hand movements; LP = light perception; NLP = no light perception; ERG = electroretinogram; EOG = electro-oculogram; CNS = central nervous system.

TABLE 3

A Review of Treatment Outcomes for Three cases of Cancer-Associated Retinopathy/Cone Retinopathy From the Current Literature

Authors and Year of Reference	Patient Age (yrs.)/Sex	Type of cancer	Initial VA and/or VF, and Other Eye Findings	Type of Treatment	Effect of Treatment on VA and/or VF	Length of Follow-Up
Cogan et al, 1990[28]	72/F	Pleomorphic uterine carcinoma	VA* Total achromatopsia; Recurrent blindness upon exposure to bright light Central scotomas OU ERG cone responses attenuated	None	Stable vision	Died 9 months later from metastases
Campo et al, 1992[23]	72/F	Primary small cell carcinoma of the endometrium	20/80 OU Central scotomas OU ERG cone responses decreased	Steroids and XRT to pelvis	No visual improvement, later HM OU	Died 6 months later from metastases
Jacobson et al, 1995[59]	87/F	Hurthle cell thyroid adenocarcinoma, gastric adenocarcinoma, colon adenocarcinoma	20/200 OU Mild optic disk pallor, diffuse retinal artery narrowing, granular macula, absent foveal light reflexes Central scotomas OU ERG cone responses attenuated	None	Stable vision	15 months

*Indicates information not available.

F = female; M = male; VA = visual acuity; VF = visual fields; ERG = electroretinogram; XRT = radiation therapy.

fected, and the presence of anti-recoverin antibodies is required for its diagnosis.[94]

As described in several case reports in the literature, the typical clinical presentation includes decreased visual acuity with vision better when wearing dark sunglasses, loss of color perception, central scotomas, and attenuated retinal vessels.[83] The electroretinogram shows absent cone responses. The neurological examination and MRI of the brain is usually normal. The cerebrospinal fluid is remarkable for only a mild lymphocytic pleocytosis.[94] Postmortem examination of the retina in one patient described by Cogan[28] revealed diffuse loss of cones, mostly in the macula with pigmented macrophages infiltrating the other layers of the retina. Jacobson and Thirkill[46] demonstrated the presence of a 23-kDa protein and a 50-kDa protein in their patient. In both of the above patients vision remained stable without any treatment (Table 2).[28,59] But in another case of cancer-associated cone retinopathy with antibodies against neuron-specific enolase, a 72-year-old woman with rare small-cell carcinoma of the endometrium continued to lose vision despite treatment with steroids and radiation therapy (Table 2).[23] Compared to CAR which often progresses to total visual loss within a few months, cancer-associated cone dysfunction appears to have a more variable course.

III. Other Autoimmune Retinopathies Mimicking the CAR Syndrome

The CAR syndrome must be differentiated from other non-paraneoplastic autoimmune-associated retinopathies that may clinically present with similar symptoms and signs. The presence of anti-recoverin antibody is not specific for the diagnosis of CAR. These antibodies can exist in patients with a CAR-like syndrome but without any underlying malignancy.

Since the discovery of the CAR syndrome, antibodies against recoverin and other retinal antigens of different molecular weights have been found in a wide spectrum of autoimmune retinopathies, even in retinal degenerative diseases. It was first hypothesized by Keltner et al[66] in 1983 that an autoimmune mechanism could play a role in the pathogenesis of retinal degenerative diseases, such as retinitis pigmentosa. He reported a 61-year-old woman with undifferentiated cervical carcinoma who took 10 months to progress to blindness. She developed ring scotomas, a flat ERG pattern, and serum antibodies reactive against normal photoreceptors. Ocular histopathology confirmed the loss of retinal photoreceptors. Her vision later improved with prednisone. Her paraneoplastic retinopathy had clinical features of slowly progressive visual loss, ring scotomas, and flat ERG pattern, which were similar to those with retinitis pigmentosa.[66] In 2000, Heckenlively et al[49] also identified anti-recoverin antibodies and other yet unidentified antiretinal protein antibodies in 10 patients who presented with clinical findings consistent with retinitis pigmentosa. This antibody-mediated inflammation in retinitis pigmentosa was supported by the strong correlation between antiretinal IgG reactivity and the retinal vascular edema seen on fluorescein angiogram.[25,50]

Furthermore, the presence of anti-recoverin antibodies is not always diagnostic of CAR syndrome. Whitcup et al[135] reported a 62-year-old woman who had rapidly progressive visual loss despite treatment with prednisone. Fundus findings revealed optic atrophy and retinal vascular attenuation, with some punctate areas of retinal pigment epithelial atrophy. Electroretinogram was flat and visual fields showed mild peripheral constriction. This patient had anti-recoverin antibodies suggestive of a CAR-like syndrome without any evidence of an underlying malignancy for a period of 3 years.[135]

Another group of retinopathies involves autoimmune reactions directed against the *inner* plexiform layer of the retina, as shown by indirect immunochemistry staining techniques, and not specifically against the recoverin antigen or the enolase antigen. Mizener et al[95] in 1997 described two cases of autoimmune retinopathies in which vision deteriorated very slowly, from 5–10 years, unlike the visual loss in CAR occuring over several weeks. Clinical features that were similar to CAR included photopsias, relatively normal-appearing fundi, abnormalities on electroretinogram, and the presence of an autoimmune reaction against the retina. These young patients, with a family history of autoimmune diseases and visual field defects more paracentral than ring-like, had no evidence of malignancy after follow up for at least 5 years. Although visual loss was bilateral, involvement of the fellow eye was much delayed compared to that in the CAR syndrome.[95] Peek et al[105] found that the autoimmune reaction against the *inner* retinal layer could be directed against the 35-kDa retinal Müller cell-associated antigen. He described a 67-year-old woman who presented with CAR-like symptoms and signs, but experienced slowly progressive visual loss over many years. In this particular autoimmune retinopathy the 35-kDa retinal Müller cell-associated antigen is involved in the degeneration of retinal Müller cells that maintain retinal structural integrity and ion uptake from the extracellular space. The slower effect of this cellular membrane dysfunction could have lead to a more gradual visual loss, compared to the more subacute visual loss from impaired photoreceptors and bipolar cells that could immediately block retinal signal transduction.[18]

IV. Melanoma-Associated Retinopathy

Previous attempts to explain the MAR syndrome resulted in its association with non-paraneoplastic phenomenon. This retinopathy/night-blindness syndrome was initially thought to have been induced by vincristine chemotherapy by Ripps et al[114] in 1984. Gass[40] described it as an acute Vogt-Koyanagi-Harada–like syndrome associated with metastatic cutaneous melanoma. In 1988 DuBois et al[32] reported that this retinopathy involved loss of the inner retinal layer in patients with complicated migraines. It was not until Berson et al[14] in 1988 when this form of night-blindness was finally classified as a paraneoplastic retinopathy associated with malignant melanoma.

Unlike CAR, which usually heralds the onset of a malignancy, MAR commonly presents after the melanoma is diagnosed, often at the stage of metastases, and is more common in men than in women. Out of a total of 64 cases reported in the literature so far, two patients presented with MAR before the diagnosis of melanoma and 6 before metastases (Table 4). Unlike the severe impairment of visual acuity, color vision, and central visual field in patients with CAR, patients with MAR often have near normal visual acuity, color vision (mild abnormalities in red-green axis and/or blue-yellow axis), and central visual field.[94] Patients with MAR often do not develop progression of their retinal dysfunction. Only the rods are affected. Symptoms include sudden shimmering, flickering photopsias, night blindness, and mild peripheral visual field loss. Typical signs of MAR include peripheral visual field depression or midperipheral visual field loss and a normal-appearing fundus.[10,14,16,18,20,32,40,42,64,67,73,74,93,95,105,111,113,116,121,136,137] Less commonly, a posterior uveitis, vitreous reaction, and periphlebitis can occur later.[64,65,111,116] Borkowski et al[18] in 2001 reported unusual fundus changes in two patients not previously described in association with MAR. One patient had round and oval white lesions in the outer retina and retinal pigment epithelium. The other patient had diffuse retinal pigment epithelial loss of pigment and small atrophic lesions of the retina, retinal pigment epithelium, and choroids. These fundus lesions could be part of the spectrum of presentations of MAR, but their pathological significance is still unclear.[18]

Histopathologic evidence of ganglion cell transsynaptic atrophy, a marked decrease of bipolar neurons in the inner nuclear layer with normal photoreceptor cells in the outer nuclear layer can be seen (Fig. 2).[42,102] Of all the documented cases of MAR in the literature, only one patient had normal ocular pathology.[70]

Patients with central nervous system metastases from malignant melanoma who present with visual symptoms should be evaluated for MAR syndrome. Similar abnormalities, such as congenital stationary night blindness, juvenile retinoschisis, vincristine toxicity, and central retinal artery or vein occlusion should be differentiated from MAR by history and eye examination.[57] The presence of anti-rod bipolar cell antibodies helps confirm the diagnosis of MAR when the patient has a history of malignant melanoma. Electroretinogram findings are similar to those in congenital stationary night blindness, except that the blue cones are affected in MAR.[16,42] Typical findings include a markedly reduced or absent dark-adapted b-wave, indicating bipolar and Müller cell dysfunction, with sparing of a-wave as a mostly negative-appearing scotopic response.[65] The reduced cone b-wave represents a predominant loss of "on," or depolarizing bipolar cells which subserves the rod pathway.[80,136] Neurotransmission between the rods and these depolarizing bipolar cells is impaired. The "off" or cone photoreceptors and hyperpolarizing bipolar cells are both spared.[10]

It is thought that an antibody against rod bipolar cells in the retina cross-reacts with an antigen on melanoma cells to cause failure of neural transmission from rods to inner retina.[93] Some evidence even suggest that the bipolar antigen is a lipid, not a protein.[39,97] Intravitreal injection of human MAR immunoglobulin (IgG) into monkeys leading to electroretinogram abnormalities characteristic of that in MAR syndrome patients provides further direct experimental evidence that these antibodies are directed against the "on" bipolar cell pathway.[80] Severe defects of the magnocellular pathway with sparing of the parvocellular pathways was shown by psychophysical testing. These pathways are separated on the level of the retinal bipolar cells.[136,137] Serial electroretinograms indicate no progressive retinal degeneration, but macular changes secondary to posterior uveitis contribute to the later deterioration of visual acuity.[65]

The diagnosis of MAR is based upon a positive history of malignant melanoma and the demonstration of circulating IgG autoantibodies from the patient, specifically reacting with human rod bipolar cells on immunofluorescent stains.[93,134] It is also important to note that anti-bipolar cell antibodies are not specific for MAR. These antibodies were recently found in a patient with a MAR-like syndrome without any previous melanoma. Jacobsen et al[58] described a 51-year-old woman who presented with progressive visual glare for 1 year, normal visual acuity and color vision, paracentral scotomas, and a normal fundus. Scotopic electroretinogram was flat in the right eye and decreased in the left eye. Although anti-bipolar antibodies were identified, she later was found to have colon cancer. After resection of the tumor and che-

TABLE 4

A Review of Treatment Outcomes for 64 Cases of Melanoma-Associated Retinopathy (MAR) From the Current Literature

Authors and Year of Reference	Patient Age (yrs.)/Sex	Onset of MAR Since Diagnosis of Malignant Melanoma (yrs.)	Initial VA and/or VF, and Other Eye Findings	Type of Treatment	Effect of Treatment on VA and VF	Lifespan Since Diagnosis of Melanoma (yrs.)
Gass, 1984[40]	71/F	3	LP OU	Surgery Prednisone 80 mg	20/50 OD 6/200 OS	5.1 (died)
Ripps et al, 1984[114]	30/M	1.5	20/20 OU Only night blindness Normal VF	Dacarbazine, CCNU, bleomycin sulfate, and vincristine sulfate	Stable vision	*
Berson et al, 1988[14]	69/M	2.5	20/25 OS 20/20 OS Normal VF No ERG rod response	Surgery and dacarbazine	*	4 (died)
DuBois et al, 1988[32]	38/M	MAR presented 2 years bfore malignant melanoma	20/20 OU Hemianopsia OD Macular-sparing scotoma OS ERG a-wave abnormal; photopic and scotopic b-waves normal EOG normal	None	*	*
Alexander et al, 1992[10]	58/M	15	20/25 OU enlarged blind spot and parafoveal scotoma OD; normal VF OS	Surgery and chemotherapy Prednisone 80 mg	*	*
MacKay et al, 1992[84]	*	*	*	*	*	*
Pollock et al, 1992[111]	3 cases	*	*	*	*	*
Andreasson et al, 1993[12]	48/M	MAR developed 2 years after metastatic melanoma	25/25 OU Normal VF OU	Surgery	*	*
Milam et al, 1993[93]	36/M	3.7	20/20 OD 20/40 OS Normal VF OD and central scotoma OS	Surgery; Prednisone 60 mg	Stable vision except for decreased sensation of "looking through water" and decreased "annoyance to bright lights"	*

(*continued*)

TABLE 4

Continued

Authors and Year of Reference	Patient Age (yrs.)/Sex	Onset of MAR Since Diagnosis of Malignant Melanoma (Yrs.)	Initial VA and/or VF, and Other Eye Findings	Type of Treatment	Effect of Treatment on VA and VF	Lifespan Since Diagnosis of Melanoma (yrs.)
Rush et al, 1993[118]	50/M	MAR developed 1 month after metastatic melanoma	20/40 OU general depression and nasal constriction OD; arcuate defects OS	Surgery; plasmapheresis	Progressive VF loss OU	*
Weinstein et al, 1994[134]						
Patient 1	46/F	1.3	1/200 OU	Surgery Oral prednisone and subtenon's Medrol injection	1/200 OU	7.5
Patient 2	46/F	0.2	20/20 OU	Surgery	20/30 OD 20/70 OS	*
Kim et al, 1994[73]						
Patient 1	61/M	2	20/20 OU	Surgery	*	*
Patient 2	58/M	1.5	20/40 OD 20/30 OS	Surgery; XRT; carboplatin, vinblastine, vindesine alternating with dacarbazine and vincristine	*	3 died
Patient 3	78/M	MAR developed several months after diagnosis of melanoma	20/1200 OU	Surgery; vindesine	*	5 died
Kellner et al, 1995[64]	44/M	1.8	20/40 OD 20/25 OS Concentric peripheral restriction OU progressing to central and paracentral scotoma OS	Surgery, interferon, prednisone, acetazolamide, flurbiprofen	Vision worsened and stablized at 20/400 OD 20/40 OS	5
Milam, 1995[94]	10 cases	2.2	9 had VF loss	Surgery, chemotherapy, XRT, interferon, and vaccine	*	8 died
	62/M	3.5	20/20 OU central scotomas, peripheral constriction, and enlarged blind spots OU	*	*	*
Okel et al, 1995[102]	62/M	19	20/30 OS 20/60 OS	Surgery		19.5 (died)

(*continued*)

TABLE 4

Continued

Authors and Year of Reference	Patient Age (yrs./Sex	Onset of MAR Since Diagnosis of Malignant Melanoma (yrs.)	Initial VA and/or VF and Other Eye Findings	Type of Treatment	Effect of Treatment on VA and VF	Lifespan Since Diagnosis of Melanoma (yrs.)
Remulla et al, 1995[111]	52/M	2.4	20/40 OD 20/30 OS peripheral constriction, peripheral scotomas OU; paracentral scotoma OD	Surgery Prednisone 80 mg	6/400 OD 20/40 OS	7.3
Rougier et al, 1995[116]	61/M	1.1	20/20 OD 20/25 OS Normal VF OD Tubular VF OS	Surgery, chemotherapy	20/25 OD 20/30 OS	*
Singh et al, 1995[121]	64/M	MAR developed 2 weeks before malignant melanoma	20/20 OU Constriction of nasal fields OU and inferior arcuate scotoma OD ERG scotopic b-wave response decreased	Surgery	Stable vision	*
Bret-Dibat et al, 1996[20]	60/M	1	10/10 OD 8/10 OS Full VF OD and tubular VF OS Scotopic ERG flat	None	8/10 OD 7/10 OS Tubular VF OU	*
Wolf and Arden, 1996[136]	*	*	*	*	*	*
Boeck et al, 1997[16]	51/M	4.1	20/50 OD 20/40 OS Peripheral constriction OU ERG rod response decreased	Surgery, chemotherapy, BCG, and prednisone	Stable vision	7
Kiratli et al, 1997[74]	66/M	Few days	20/30 OD 20/60 OS Arcuate defects OU	Surgery, chemotherapy	No improvement	1 (died)
Gittinger and Smith, 1999[42]	59/M	5	20/30 OD 6/200 OS Peripheral constriction OD and central scotoma OS	Surgery, interleukin-2, interferon, and XRT	Stable vision	5.7 (died)
McCoy and Hedges, 1999[92]	55/M	1	20/20 OD 20/60 OS Paracentral scotoma OD, central depression OS	Surgery, prednisone, azathioprine and gabapentin	Improved VF and ERG OD	*
Potter et al, 1999[110]	61/M	3	10/200 OD 20/200 OS Central scotomas and peripheral constriction OU	Surgery, chemotherapy	4/200 OD 1/ 200 OS	5

(*continued*)

TABLE 4

Continued

Authors and Year of Reference	Patient Age (yrs.)/Sex	Onset of MAR Since Diagnosis of Malignant Melanoma (Yrs.)	Initial VA and/or VF and Other Eye Findings	Type of Treatment	Effect of Treatment on VA and VF	Lifespan Since Diagnosis of Melanoma (yrs.)
Feigl et al, 2000[36]	67/M	1	20/25 OD 20/30 OS peripheral constriction, central and paracentral scotoma OU	Surgery, interferon-alpha, isotretinoin	No improvement	2 (died)
Flynn et al, 2000[38]	1 case	*	*	*	*	*
Holder, 2000[52]	7 cases	*	*	*	*	*
Haus, 2000[48]						
Patient 1	51/M	*	*	*	*	*
Patient 2	62/M	*	*	*	*	*
Patient 3	77/M	*	*	*	*	*
Lei et al. 2000[80]	1 case	*	*	*	*	*
Vaphiades et al,	57/M	*	20/25 OU peripheral constriction OU	Cytoreductive surgery, alpha postmetastatic tumor removal, IVIg for 5 days	20/25 OD 20/30 OS improved color vision and VF photopsia resolved	3
Borkowski et al, 2001[18]						
Patient 1	47/F	*	*	*	*	*
Patient 2	57/M	*	*	*	*	*
Keltner et al, 2001[70]						
Patient 1	39/F	0.5	20/25 OD 20/20 OS central scotomas OU	Cytoreductive surgery Prednisone 60 mg for 2 months	Improved color vision, VF and dark adaptation	3.5
Patient 2	68/M	13	CF 3' OU Central scotomas and peripheral constriction OU	Surgery	No improvement	15
Patient 3	78/F	2	20/30 OD 20/25 OS central scotomas, arcuate defects and peripheral constriction OU	Surgery	20/20 OU	5

(*continued*)

TABLE 4

Continued

Authors and Year of Reference	Patient Age (yrs.)/Sex	Onset of MAR Since Diagnosis of Malignant Melanoma (yrs.)	Initial VA and/or VF, and Other Eye Findings	Type of Treatment	Effect of Treatment on VA and VF	Lifespan Since Diagnosis of Melanoma (yrs.)
Patient 4	47/M	7	20/20 OU peripheral constriction OS>OD	Surgery, interleukin, XRT, and chemotherapy IVIg for 5 days	20/20 OU	8 (died)
Patient 5	76/F	3	20/50 OU peripheral constriction OU	Surgery		4
				IV methylprednisolone 125 mg BID, plasmapheresis ×5 days, the oral prednisone taper	20/60 OU VF improved then returned to baseline	
Patient 6	42/M	MAR presented 4 months before metastatic melanoma	20/20 OU arcuate defects and peripheral constriction OD: double arcuate defects and peripheral constriction OS	Cytoreductive surgery	20/20 OD 20/40 OS improved VF	4.3
Patient 7	75/M	3.5	20/20 OU peripheral constriction and depression OU	Cytoreductive surgery		4.5
				Prednisone for 10 days without improvement then IVIg 200–220 g/month for 9 months	Improved VF and visual symptoms	
Patient 8	*	*	*	*	*	*
Patient 9	M	*	*	*	*	*
Patient 10	M	*	*	*	*	*
Patient 11	F	*	*	*	*	*

*Indicates information not available.
F = female; M = male; VA = visual acuity; VF = visual fields; ERG = electroretinogram.
Portions of this table have been adapted from Table 1 and Table 2 in Keltner et al.[70]

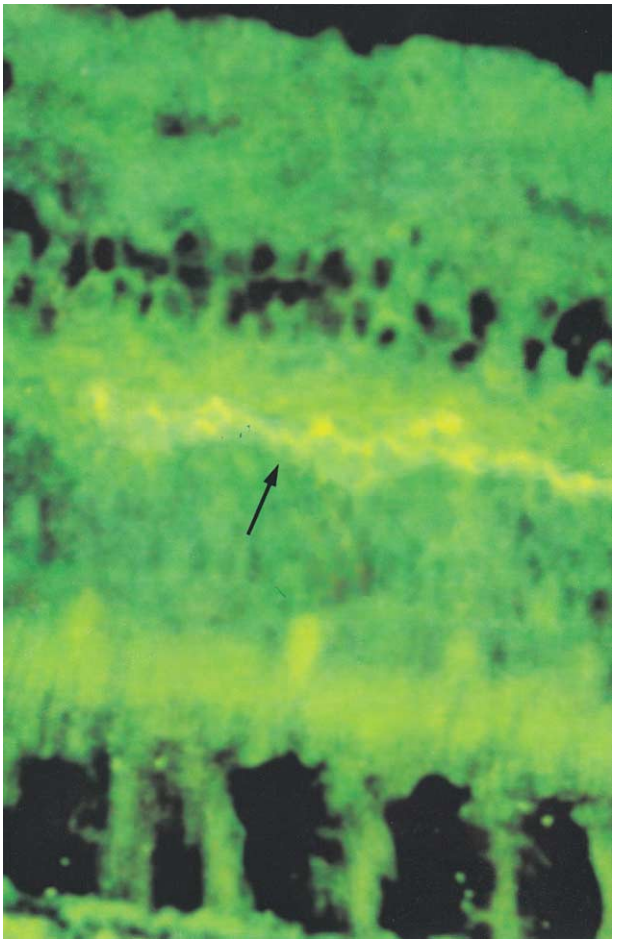

Fig. 2. Indirect immunofluorescence stain showing autoantibody reactions (arrow) with retinal bipolar cells between the inner and outer nuclear layers in a patient with melanoma-associated retinopathy (original magnification × 160) (Reprinted from Boeck K et al[16] with permission of *British Journal of Dermatology*.)

motherapy, no anti-bipolar antibodies were detected and her scotopic electroretinogram responses significantly improved.[157]

Based on the reported cases of MAR reviewed in the current literature, steroids did not improve vision in 3/64 patients[10,16,36] (Table 4). In 3/64 patients[65,93,111] steroids helped to decrease haze and improve retinal phlebitis. In only one patient with probable MAR syndrome, published by Gass in 1994[40] as having Vogt-Koyanagi-Harada (VKH) syndrome, did steroids dramatically improve visual acuity. Plasmapheresis alone was ineffective in one patient,[118] but plasmapheresis, oral prednisone, azathioprine, and gabapentin together improved the visual fields and ERG in one patient (McCoy D: Ocular Surgery News, Feb 1 1999). These ineffective treatments could be the result of irreversible immunologic damage to cells.

Keltner, Thirkill, and Yip[70] recently introduced a new treatment strategy to improve vision in patients with MAR which involves cytoreduction with surgery or radiation followed by adjuvant immunotherapy to decrease the tumor burden. Cytoreduction of metastases by radiation therapy improved vision in one patient.[94] They were the first to show that early treatment with IVIg improved the visual acuity and visual fields of patients with MAR. IVIg alone improved the visual acuity in one patient, but IV methylprednisolone and plasmapheresis both improved the visual acuity and visual field of one patient.[70] Cytoreductive surgery improved the color vision and visual field in one patient and the visual acuity and visual field in another.[70] Both IVIg and cytoreductive surgery were effective in improving the color vision, visual field, and visual symptoms of one patient[132] and the visual field of another patient.[121] Newer adjuvant immunotherapies with the combination of CancerVax/bacilli Calmette-Guerin (BCG) and GM1 ganglioside/BCG vaccine have increased survival rate in patients with metastatic melanoma.[81] Another promising therapy involves autologous tumor cells transfected with interleukin-2 genes that are used as a vaccine to generate an immune response against the tumor cells.[104]

V. Paraneoplastic Optic Neuropathy Syndromes

Paraneoplastic ophthalmologic syndromes are usually retinopathies and rarely optic neuropathies. Only 18 cases of paraneoplastic optic neuropathies have been reported in the literature so far (Table 5). Paraneoplastic optic neuropathy is a subacute, progressive, usually bilateral visual loss not associated with pain. The optic disk is normal or edematous and can involve the optic chiasm. Direct compression or infiltration of the optic nerve and acute ischemic optic neuropathy should be ruled out.[57]

Optic neuropathy, as part of a paraneoplastic brainstem or cerebellar syndrome, has been reported in patients with small-cell lung carcinoma,[15,17,31,82,87,133] Hodgkin's and non-Hodgkin's lymphoma,[29,112] neuroblastoma,[71] pancreatic glucagonoma,[79] nasopharyngeal carcinoma,[51] bronchial carcinoma,[106] and most recently, thymoma (Table 5).[140] Most cases present with bilateral optic disk edema and improve with treatment of the cancer (Table 6).[15,29,31,71,79,82,87,133,140] Neuropathological findings have shown either nonspecific perivascular inflammation,[17,79,106,140] axonal loss or demyelination of the optic nerve (Fig. 3).[17,87,106,140] Pillay et al[106] reported a case of bilateral visual loss in a 56-year-old man who had bronchial carcinoma. He had bilateral optic disk edema and internuclear ophthalmoplegia. Neuropathological findings revealed that he had secondary demyelination of the medial longitudinal fasciculus with nonspecific lymphocytic infiltration and adhesive arachnoiditis of the optic nerve without any evidence of central nervous sys-

TABLE 5

Frequency of Malignancies Associated with Paraneoplastic Optic Neuropathies

Types of Malignacies Associated with Paraneoplastic Optic Neuropathies	Number of Reported Cases in the Current Literature
Lung[15,31,82,87,124,133]	6
Bronchial[106]	1
Nasopharyngeal[51]	1
Neuroblastoma[71]	1
Lymphoma[29]	1
†	† 8/116 patients with lung cancer, thymoma, other malignancies who tested positive for CRMP-5 developed optic neuropathies

†Specific data for individual patients were not available in the study done by Yu et al.[140]

tem metastasis.[106] In contrast, other cases of paraneoplastic brainstem or cerebellar syndromes showed specific demyelination of the optic nerve, in addition to brainstem gliosis and glial nodule formation and perivascular lymphocytic infiltration without vasculitis affecting small arterioles in the cranial nerve nuclei, the inferior olivary nuclei, the vestibular nuclei, the basis pontis, or the substantia nigra.[17,31,87,106,140] Optic neuropathy can be associated with a subacute paraneoplastic cerebellar syndrome with an underlying small-cell lung carcinoma. Neurological signs may include dysarthria,[31,82] ataxia,[31,140] downbeat nystagmus,[87] horizontal gaze-evoked jerk nystagmus[82] from cerebellar degeneration, pain, numbness, and absent deep tendon reflexes from a sensory peripheral neuropathy.[13,82,140] De la Sayette et al[31] in 1998 identified a novel autoantibody in a paraneoplastic cerebellar syndrome with optic neuropathy that was associated with small-cell lung carcinoma. This optic neuropathy was identified in only 1 of 12 patients with anti-CV2 antibody-related paraneoplastic syndromes. Anti-CV2, a 66-kDa protein, is the only paraneoplastic autoantibody reported to bind exclusively to oligodendrocytes. The patient was a 62-year old man who had simultaneously developed a severe cerebellar syndrome and bilateral painless visual loss greater in the left eye than in the right. Funduscopic examination revealed bilateral disk edema and fluorescein angiography showed marked leakage in the area of the optic disks, also greater in the left eye than in the right. The CV2 antigen was found to be expressed by oligodendrocytes of the cerebellum, brainstem, spinal cord, and optic chiasm. Although a pathological examination was not performed, an immune-mediated secretion or a toxic secretion of cytokines, rather than demyelination, was thought to explain the clinical findings.[31] Nonspecific inflammatory changes and diffuse loss of cerebellar Purkinje cells were seen in previously reported cases involving anti-CV2 antibodies.[54,116] CRMP-5 is another recently characterized autoantibody associated with paraneoplastic optic neuropathy in small-cell lung carcinomas, and rarely thymomas. This IgG is directed against a 62-kDa neuronal cytoplasmic protein of the collapsin response-mediator family. CRMP-5 is expressed in adult central and peripheral neurons, including synapses, and in small-cell lung carcinomas, and rarely in thymomas. The CRMP family of proteins is believed to mediate growth guidance cues during neurogenesis. The CRMP-5 antibody is as frequent as anti-Yo antibody and second in frequency to anti-Hu antibody. The neurological deficits include chorea, cranial neuropathies, peripheral neuropathy, autonomic neuropathy, cerebellar ataxia, subacute dementia, and neuromuscular junction disorders. It is not associated with any specific neurological syndrome. While 8 of 116 CRMP-5 seropositive patients had optic neuropathy, only three of the eight presented with optic neuropathy at the onset of the illness.[140]

Treatment of the specific cancer in paraneoplastic optic neuropathy patients with chemotherapy and/or radiation therapy resulted in significant visual improvement (Table 6).[15,17,29,31,51,71,79,82,87,106,133,140] Vision recovered to normal or near normal with improvement of visual fields in 8/11 patients (Table 6).[15,29,31,51,82,87,133] Hoh et al[51] showed that treatment with steroids alone also improved vision in a patient with paraneoplastic optic neuropathy and nasopharyngeal cancer. The visual defects improved with an increase in prednisolone and worsened with its decrease (Table 6).[51]

VI. The Spectrum of Autoimmune Retinopathies and Optic Neuropathies

The spectrum of autoimmune retinopathies and optic neuropathies have recently been termed autoimmune-associated retinopathy and optic neuropathy (ARRON) syndrome by Keltner, Thrikill, and Yip.[70] There is evidence to suggest overlap syndromes

TABLE 6

A Review of the Treatment Outcomes in 18 Cases of Paraneoplastic Optic Neuropathy From the Current Literature

Authors and Year of Reference	Pt. Age (yrs.)/Sex	Type of Cancer	Initial VA and/or VF and Other Eye Findings	Type of Treatment	Effect of Treatment on VA and VF	Length of Follow-up
Pillay et al, 1984[106]	56/M	Mixed cell bronchial carcinoma	VA* VF* Internuclear ophthalmoplegia OU and optic neuritis OS	None	*	Died 9 mos. later from sepsis; no autopsy done
Waterston et al, 1986[133]	58/M	Small cell lung carcinoma	6/24 OD 6/6 OS Optic neuritis and external ophthalmoplegia OU VF*	Prednisolone	6/8 OD 6/6 OS VF*	Died 9 mos. later without clinical evidence of metastases; no autopsy done
Kennedy et al, 1987[71]	21/M	Neuroblastoma	Poor VA OU Disk edema OU Slight enlargement of blind spots OU	Dexamethasone, cyclophosphamide, doxorubicin, VP16-213, alternating with cisplatin, vinblastin, and bleomycin for a total of 6 courses	Normal vision	5 mos.
Coppeto et al, 1988[29]	52/M	Chronic lymphomatous meningitis secondary to paranasal sinus lymphoma	CF at 2 feet OD 20/30 OS Optic disk edema OU Generalized constriction of VF	Prednisone and chemotherapy	20/20 OU	Died 14 mos later from pneumonia and pleural effusion, no autopsy done
Hoh et al, 1991	31/M	Nasopharyngeal carcinoma	Poor VA OU Optic neuritis OS Sectorial VF defect OS	ACTH 80 U/day tapered to 10 U/day	6/6 OU Inferior arcuate defect OS	20 mos.
				Prednisolone 30 mg/day tapered to 10 mg/day and retrobulbar methylprednisolone 40 mg injection	Improved VF	
				Prednisolone 20 mg/day then discontinued	Scotoma extending to temporal hemianopsia OS and normal VF OD	
				Prednisolone 25 mg/day	Resolved scotoma OS	
				Optic canal decompression OS	Inferior altidunial defect OS	

(*continued*)

TABLE 6

Continued

Authors and Year of Reference	Pt. Age (yrs.)/Sex	Type of Cancer	Initial VA and/or VF and Other Eye Findings	Type of Treatment	Effect of Treatment on VA and VF	Length of Follow-up
				Prednisolone 60 mg/day	Nasal step defect OS	
				Prednisolone 20 mg/day	Arcuate defect OS	
				Prednisolone 15 mg/day	Enlarged blind spot OS contiguous with inferior nasal scotoma OS then worsened VF OS	
Malik et al, 1992[87]	63/M	Undifferentiated small cell lung carcinoma with subacute cerebellar degeneration	20/200 OU Cecocentral scotomas and generalized peripheral constriction OU	XRT to mediastinum then chemotherapy	Stable vision after 6 months	Died 20 mos. later from metastases; confirmed on autopsy
Blumenthal et al, 1998[15]	72/F	Small cell lung carcinoma	Poor VA OU Disk edema OU severe peripheral constriction OU	4 cycles of chemotherapy	Normal vision	16 mos.
De la Sayette et al, 1998[31]	62/M	Small cell lung carcinoma	20/25 OD 20/400 OS Central scotomas OU	Cisplatin, etoposide, mediastinal and subclavicular XRT	20/20 OU Normal VF OD and central scotoma OS	23 mos.
Luiz et al, 1998[82]	59/F	Small cell lung carcinoma	20/30 OD 20/40 OS Disk edema OU Severe peripheral constriction OU	Solumedrol 6 cycles of cisplatin and VP16, pulse Solumedrol	Improved vision 20/20 OD 20/25 OS Optic atrophy OU Improved VF	9 mos.
Yu et al, 2001[140†]	*	*	*	*	*	*
Thambisetty et al, 2001[124]	72/F	Small cell lung carcinoma	20/60 OU Disk edema OU	*	20/400 OU Central scotomas OU Disk edema OU	3 mos.

*Indicates information not available.

Pt = patient; F = female; M = male; VA = visual acuity; VF = visual fields; ERG = electroretinogram; XRT = radiation therapy.

†Data for individual patients were not available in the study by Yu et al.[140] 8/116 patients with lung cancer, thymoma, or other malignancies who tested positive for CRMP-5 developed optic neuropathies.

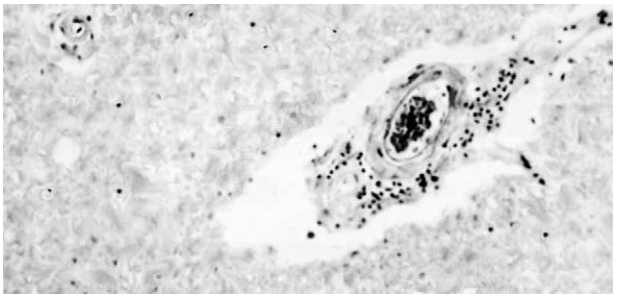

Fig. 3. Hematoxylin-phloxine-saffron stain of the right optic nerve showing mild axonal loss and demyelination in a patient with paraneoplastic optic neuropathy associated with thymoma (original magnification × 10).

between paraneoplastic retinopathies and optic neuropathies. A specific autoimmune reaction to a 22-kDa neuronal antigen was demonstrated in both the retina and optic nerve of patients who had retinal degeneration from various causes, including paraneoplastic retinopathy, macular degeneration, retinitis pigmentosa, and diabetic retinopathy. One of the 8 patients in this study by Keltner et al[67] 1999 had the MAR syndrome. Furthermore, superimposed autoimmune reaction against a 57-kDa antigen in the RPE can also be found in some patients with visual loss due to either paraneoplastic or non-cancer related retinal degenerations.[125]

Paraneoplastic eye disorders represent only part of a spectrum of autoimmune retinopathies and optic neuropathies. The specific antibodies most commonly associated with CAR are not present in all affected patients. A vast array of retinal antibodies involved in these autoimmune retinopathies and optic neuropathies still remain to be identified. The anti-recoverin antibodies in the CAR syndrome may also be detected in other autoimmune-mediated retinal degenerations, such as retinitis pigmentosa.[25,49,50] Based upon current evidence in the literature, these autoimmune reactions in CAR may all lead to a common pathway of retinal degeneration by apoptosis.[6]

Like the CAR syndrome, the MAR syndrome demonstrates diverse clinical and immunological features. The demonstration of circulating IgG antibodies reacting with human rod bipolar cells on immunofluorescent stains is considered diagnostic for the MAR syndrome in a patient who was or will shortly be diagnosed with malignant melanoma. However, anti-bipolar cell antibodies have also been recently identified in retinopathies associated with other cancers, such as colon cancer.[58,93] Just as an increasing array of antibodies are being characterized in the CAR syndrome, the trend toward finding other antibodies in the MAR syndrome will also ensue.

Compared to CAR and MAR, the autoimmune optic neuropathies improve with steroids and appear to have better overall visual prognosis. These demyelinating optic neuropathies involve reversible inflammatory changes that do not appear to lead to degenerative pathways. Steroids transiently improve vision in patients with CAR, but most continue to progress to total visual loss within several months.[14,16,32,49,50,83,95,105,114] Recent data suggest that therapy for the MAR syndrome, cytoreduction by surgery or radiation followed by adjunctive immunotherapy, can improve certain aspects of vision.[70,94,132] The long-term stability of this visual outcome and overall prognosis for metastatic melanoma are unknown until longer follow-up data are collected on these patients.

The literature so far has only case reports documenting the treatment outcomes of various conventional agents, such as steroids. Future evaluation of potential immunotherapies, such as IVIg and vaccines, for autoimmune retinopathies and optic neuropathies will need to be tested systematically in clinical trials.

Method of Literature Search

The literature was searched by MEDLINE (up to December 2001). Broad subject searches were conducted with headings related to autoimmune retinopathies, autoimmune optic neuropathies, melanoma-associated retinopathies, cancer-associated retinopathies, and paraneoplastic optic neuropathies. Citations within material obtained from the Medline search were also used. Walsh and Hoyt's *Clinical Neuro-ophthalmology* text also provided information.

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Outline

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