Autoimmune Retinopathy and Paraneoplastic Syndromes

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Abstract

Autoimmune retinopathies and paraneoplastic retinopathies are rare ocular syndromes that can signal the presence of an underlying autoimmune condition or systemic malignancy. This chapter will present the pathogenesis, diagnostic features, and management strategies for cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), and autoimmune-related retinopathy and optic neuropathy (ARRON).

Keywords

Autoimmune-related retinopathy and optic neuropathy • Cancer-associated retinopathy • Melanoma-associated retinopathy • Paraneoplastic syndromes • Optic neuropathy • Vision loss

Introduction

Autoimmune retinopathy includes three main forms: cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), and nonneoplastic autoimmune-related retinopathy and optic neuropathy (ARRON). Autoimmune retinopathies encompass ophthalmic disorders in which autoantibodies are directed at various retinal components and lead to progressive vision loss. If evaluation reveals an underlying malignancy, it is considered a paraneoplastic syndrome. Although paraneoplastic syndromes occur in 10–15% of cancer patients [1], the incidence of paraneoplasia-induced antiretinal antibodies is considered rare. Without confirmed malignancy, patients with retinal dysfunction related to antiretinal antibodies are considered to have ARRON or nonneoplastic autoimmune retinopathy (npAIR). The differential for nonneoplastic cases of antiretinal autoantibodies usually includes inherited retinal degenerations [2, 3], as well as occult malignancies. This chapter will review and provide illustrative cases of CAR, MAR, and ARRON.

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Paraneoplastic Retinopathy: Cancer-Associated Retinopathy (CAR)

Cancer-associated retinopathy (CAR) is a paraneoplastic retinopathy in which autoantibodies are directed against retinal antigens causing retinal dysfunction and retinal cell death. CAR is believed to be the most common form of paraneoplastic retinopathy, although the exact prevalence has not been reported in the literature. Typically, older adults are affected, and the incidence is equal among men and women [4]. The malignancy most commonly associated with CAR is small cell lung cancer, followed by gynecologic and breast cancers [4]. Less commonly, cases have also been associated with non-small lung cancer, Hodgkin's lymphoma, bladder, prostate, pancreatic, laryngeal, and colon cancers [4].

Malignancies associated with CAR:

- Small cell lung cancer
- Gynecologic malignancies: endometrial, uterine, and cervical
- Breast
- Lymphoma
- Colon
- Prostate
- Bladder
- Laryngeal
- Pancreatic
- Metastases of unknown primary

CAR was first described in 1976 by Sawyer et al. in three patients with small cell lung cancer with progressive vision loss and has since become an increasingly recognized clinical disorder [5].

A humoral immune reaction leading to photoreceptor destruction is the most likely underlying etiology for CAR. McGinnis et al. in 1995 proposed that CAR may be initiated with a p53 tumor suppressor gene mutation in the tumor cells [6]. This mutation subsequently turns on production of the recoverin protein with the cell line becoming cancerous due to loss of the tumor suppressor activity. The human gene for recoverin protein and the p53 gene have both been localized to chromosome 17 in proximity of one another [6]. Recoverin is a calcium-binding protein located within retinal photoreceptor cells and bipolar cells and is highly immunogenic and leads to anti-recoverin antibody production [4, 7]. The anti-recoverin antibodies bind to recoverin molecules in the photoreceptor cells by penetrating the blood–retina barrier [1]. The inactivated form of retinal recoverin then causes closure of ion channels, depolarization of cells, and photoreceptor death. Specifically, anti-recoverin antibody is likely incorporated into photoreceptor cells and modulates increased phosphorylation of rhodopsin, which increases the intracellular level of calcium and the activation of caspase-dependent apoptosis, ultimately leading to photoreceptor death [1, 4, 6]. Adamus et al. in 1998 demonstrated this concept with the injection of anti-recoverin antibodies intravitreally in rats, which caused flattening of both the a and b wave on ERG and triggered photoreceptor cell death [7].

In 1987, Thirkill et al. elucidated the autoimmune etiology of CAR by identifying antiretinal antibodies via immunofluorescence [1, 8]. These autoantibodies were demonstrated to be reactive with photoreceptor outer segments as well as retinal ganglion cells [1, 8]. The 23-kDa protein recoverin, which is a calcium-binding protein found in both rods and cones, is the most frequently identified antigen in CAR [1, 8]. The second most common autoimmune retinal antibody is a 46-kDa (anti-enolase) protein, followed by 45 and 60 kDa [4]. Antibodies against 65-kDa heat shock protein 70, 44, 43, and 63 kDa have also been identified [1]. Antibodies to TULP-1 (tubby-like protein 1) protein are directed against the inner segment of photoreceptor cells, which is in contrast to anti-recoverin antibodies that are directed against the outer segments of these cells [4]. The anti-TULP-1 protein has been identified in a CAR patient with endometrial cancer [4]. Antibodies against the photoreceptor cell–specific nuclear receptor (PNR) gene product have also been reported in a case of CAR secondary to lung cancer [4]. In addition, combined paraneoplastic retinopathy with vitreous cells and optic neuritis has been associated with CRMP-5-IgG antibody, which has a 77% association with small cell lung cancer [9].

Histopathologically, CAR demonstrates diffuse photoreceptor degeneration of both rods and cones with loss of nuclei from the outer nuclear layer [1, 4]. The retinal pigment epithelium and choriocapillaris are well preserved, and ganglion cells in the inner retina, optic nerve, and geniculocalcarine pathway are all spared [1, 4, 10]. In addition, there may also be a secondary cellular response with inflammatory infiltrates being sporadically reported in CAR [1, 4].

In terms of clinical symptoms, patients may present with progressive bilateral visual loss over weeks to months. Entoptic symptoms such as flashing or flickering lights, swirling vision, or other positive visual phenomenon are often prominent [1, 4]. Patients may also report transient dimming of vision [4]. CAR affects both rods and cones. Clinical problems associated with rod dysfunction include nyctalopia, prolonged dark adaptation, midperipheral ring scotomas, and peripheral visual field deficits [4]. Cone dysfunction can present with photosensitivity, reduced visual acuity, prolonged glare after light exposure, decreased color perception, and central scotomas [4]. Visual symptoms may precede diagnosis of a systemic malignancy in 50% of patients [1]. Early in the disease, fundus examination may appear normal [1]. However, characteristic changes may occur over time with disease progression and include attenuation of arterioles, thinning and mottling of the retinal pigment epithelium, and optic disk pallor [1, 4, 5, 11]. Anterior chamber and vitreous cells, periphlebitis, and arteriolar sheathing may also be present particularly late in the course of disease [1, 4, 5, 11].

Early diagnosis of CAR may be complicated due to subtle clinical findings, and maintaining a high index of clinical suspicion is warranted. Ancillary testing can include a Goldmann visual field test, which may indicate peripheral field or central deficits [1]. Optical coherence tomography (OCT) may demonstrate extensive photoreceptor loss, and fluorescein angiography can help exclude other clinical entities as potential causes of vision loss. Fluorescein findings are usually normal, but may demonstrate mild peripheral vascular leakage consistent with vasculitis in occasional cases [12]. The most sensitive test in detecting retinal dysfunction associated with CAR is often electroretinography (ERG), in which findings are usually abnormal in the majority of cases [1]. Patients with a predominant rod or cone dysfunction show abnormal scotopic or photopic patterns, respectively [1]. In both scotopic and photopic conditions, a and b waves are depressed [1, 5, 13]. Along with ERG findings, a diagnosis of CAR can also be made by the demonstration of antiretinal antibodies using western blot analysis, immunofluorescent antibody assays, and enzyme-linked immunosorbent assay (ELISA) [1].

Results of ERG and antibody testing are not always definitive, and in patients suspected of CAR, an extensive evaluation for a malignancy should be initiated. A complete physical examination, including pelvic and breast examination for women, is recommended. A chest radiograph should initially be obtained. If normal, a chest CT scan should be performed for further evaluation [12]. Additional imaging studies for a possible malignancy include CT of the abdomen and pelvis, mammography, and total-body positron emission tomography (PET) [12]. Further evaluation for metastatic disease as the source of vision loss should also include contrast-enhanced MRI of the head and orbits and lumbar puncture for cytologic examination. Cerebrospinal fluid analysis in CAR often reveals a nonspecific finding of a mild lymphocytic pleocytosis and an increased concentration of protein [4].

The differential diagnosis in the setting of subacute unilateral or bilateral vision loss and the presence of retinal dysfunction includes paraneoplastic syndromes (CAR and MAR), npAIR (hereditary retinal degenerations and ARRON), and toxic retinopathy [12]. Etiologies for toxins include mellaril, chloroquine, and plaquenil. The time course of progression of visual symptoms is usually over years with hereditary retinopathies and weeks to months with acquired disease. Furthermore, the presence of antiretinal antibodies will also facilitate the diagnosis of autoimmune retinopathy, and evaluation for malignancy will distinguish between paraneoplastic conditions and npAIR. Specifically, npAIR can include

hereditary retinal diseases such as retinitis pigmentosa (RP), which may also have antiretinal antibodies. In a study of 116 RP patients, 43 (37%) of patients demonstrated antibodies reacting with donor eye retinal antigens on indirect immunofluorescence [2, 3, 14]. A prospective study also demonstrated that 90% of patients with RP and cystoid macular edema have antiretinal antibodies compared with 13% of RP patients without CME and 6% of controls [2, 14, 15]. However, the pathogenic role of these antiretinal antibodies in hereditary disorders remains unclear. Overall, antiretinal antibodies may be useful in helping to identify a broad spectrum of autoimmune retinopathies.

Additional diagnostic considerations for clinical symptoms similar to CAR include a retrobulbar optic neuropathy in which patients present with vision loss and a normal fundus examination. Etiologies can include ischemia, demyelinating disease, compressive lesions, toxicity, and hereditary disorders [12]. Cancer-associated cone dysfunction and toxic nutritional and hereditary optic neuropathy can also present with findings similar to CAR, such as bilateral central vision loss, central scotomas, and reduced color vision. In order to evaluate for these etiologies, additional history regarding possible alcohol, tobacco, toxic medication use, dietary patterns, and a family history of similar problems is warranted [12].

In the majority of CAR cases, the visual prognosis is often guarded, and various immunotherapies have resulted in mild to moderate visual recovery. Treatment of the underlying systemic malignancy with chemotherapy, radiation therapy, and surgery has not been shown to alter the visual prognosis [4, 16, 17]. Initial treatment for CAR usually involves modulation of the immune system with steroids. The most widely reported therapy consists of 250 mg of intravenous methylprednisolone four times daily or 60–80 mg of oral prednisone daily, followed by a slow taper to a low maintenance dose [18, 19]. Several case reports have described mild to moderate transient improvement in visual acuity and visual fields in CAR patients with high-dose intravenous methylprednisolone treatment [4, 19–21]. Keltner et al. in 1992 described a patient with improvement and stabilization of visual function and reduced antibody levels during 7 months of corticosteroid therapy; this patient died 7 months after the diagnosis of CAR [19, 22]. However, the beneficial effect of oral steroids has been limited in other reports [23–25]. Treatment with plasmapheresis alone did not prevent progression of visual loss in a patient with CAR [22, 26]. Murphy et al. reported that plasmapheresis in conjunction with oral corticosteroid therapy resulted in vision improvement, but the recovery lasted only 4 months [22, 24]. In another report, Guy and Aptsiauri reported the results of three patients with CAR treated with intravenous immunoglobulin therapy [16]. One patient had improvement in both visual acuity and visual fields; one had improvement in only visual field defects; and the other only had stabilization of vision [4, 16]. In 2007, a report of the treatment with alemtuzumab for CAR and paraneoplastic optic neuropathy described maintenance of visual acuity and visual fields during an 8-year follow-up period [22]. Currently, it remains unclear whether initiating immunomodulatory therapy prior to diffuse degeneration of photoreceptors may improve or stabilize visual acuity. Overall, due to the high mortality rate of CAR patients, observation of any definitive long-term effects of treatment on both retinal structure and visual function remains limited.

CAR Cases

CAR can present with heterogeneous clinical and diagnostic findings. Although the most common reported antigen associated with CAR is recoverin [27], three CAR cases are described with several unique clinical features and without the presence of anti-recoverin antibodies. In case 1, CAR signaled the presence of metastatic esthesioneuroblastoma, an uncommon association with paraneoplastic retinopathy. Antiretinal antibodies were not detected in this case. Cases 2 and 3 present more frequently reported malignant associations, breast cancer and small cell lung cancer. Anti-enolase antibody was positive in association with breast cancer, and CRMP-5-IgG

was detected in the small cell lung cancer case. These cases highlight that CAR facilitated the diagnosis of a systemic malignancy, clinical symptoms may be variable and subtle, and patients may have a variety of antiretinal antibody activity (see Figs. 15.1, 15.2, 15.3, 15.4, and 15.5).

CAR Case 1: CAR Secondary to Esthesioneuroblastoma (Olfactory Neuroblastoma)

A 58-year-old white female with a history of esthesioneuroblastoma treated with prior surgical resection and radiation therapy 6 months earlier

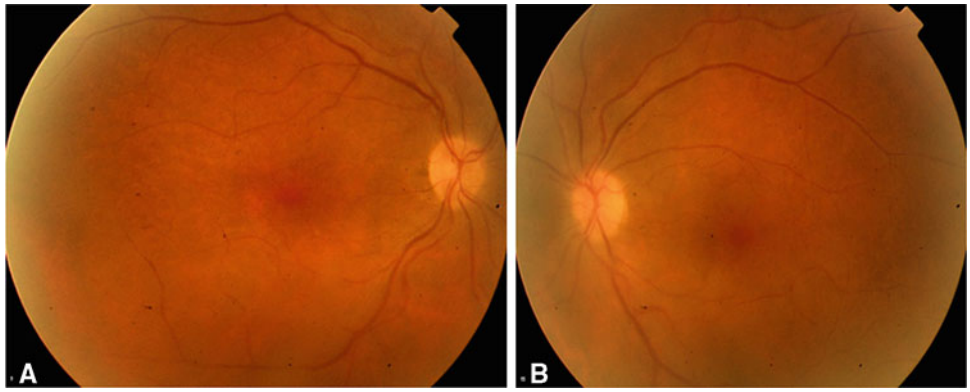


Fig. 15.1 CAR case 1: fundus photos (**a**) OD and (**b**) OS demonstrate trace disk edema OU, mild narrowing of the arterioles and venules, and a hazy media secondary to vitritis

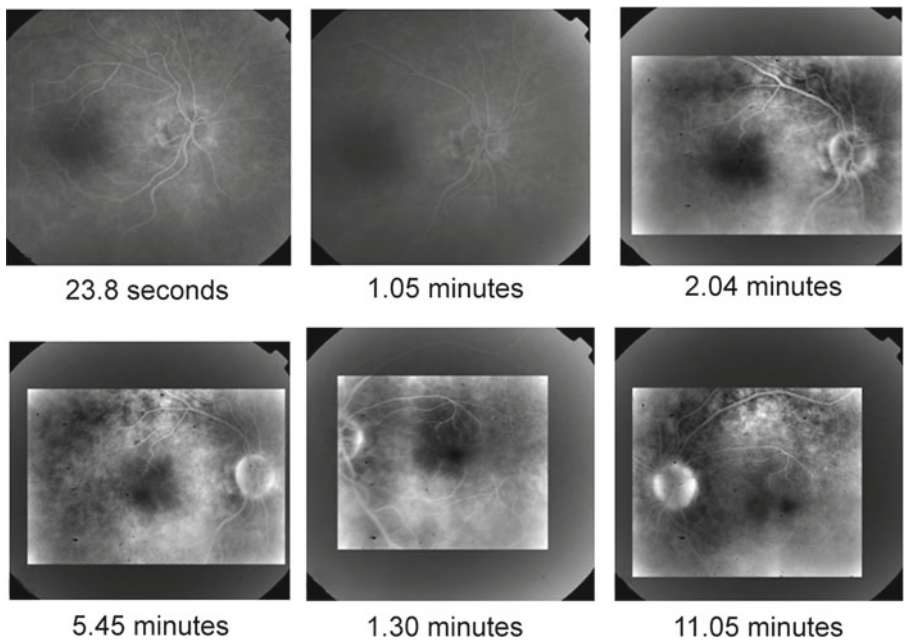


Fig. 15.2 CAR case 1: fluorescein angiography demonstrates mild perivascular leakage in both eyes with increased optic nerve fluorescein. Atypical for dense vitreous cellular reaction on an immunologic basis, there is no appreciable macular edema

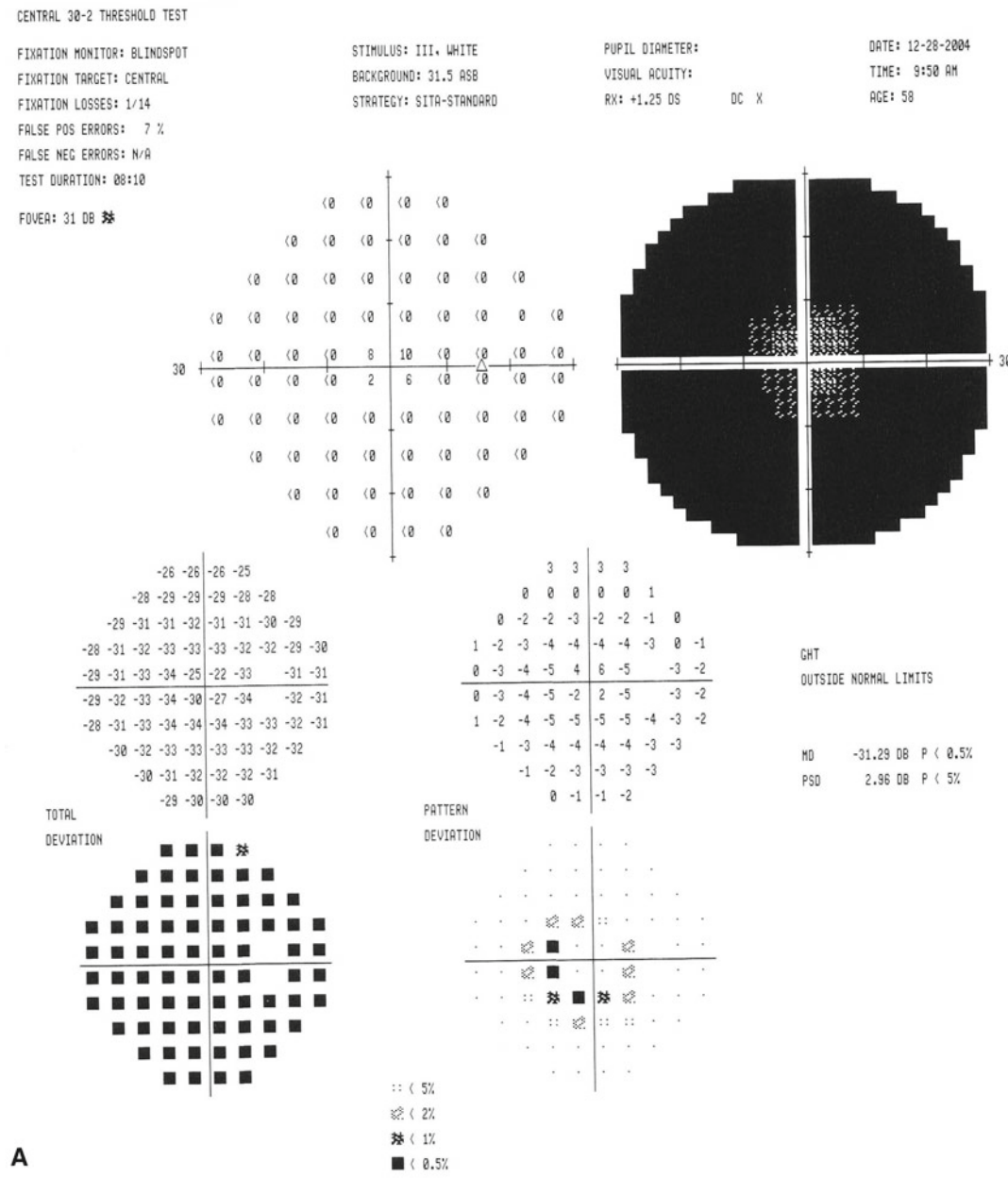


Fig. 15.3 CAR case 1: Humphrey visual fields (**a**) 30–2 OD and (**b**) OS demonstrate global depression of retinal sensitivity

presented with a 2-week history of gradually decreasing vision greater in the right than left eye. Best corrected visual acuity was 20/25 OD and 20/30 OS. Clinical examination demonstrated no afferent pupillary defect, +3 vitreous cells OU with +1 disk edema in both eyes (Figs. 15.1a, b and 15.2a–e). ERG and visual fields were markedly abnormal in each eye (Figs. 15.3a, b, 15.4a, b,

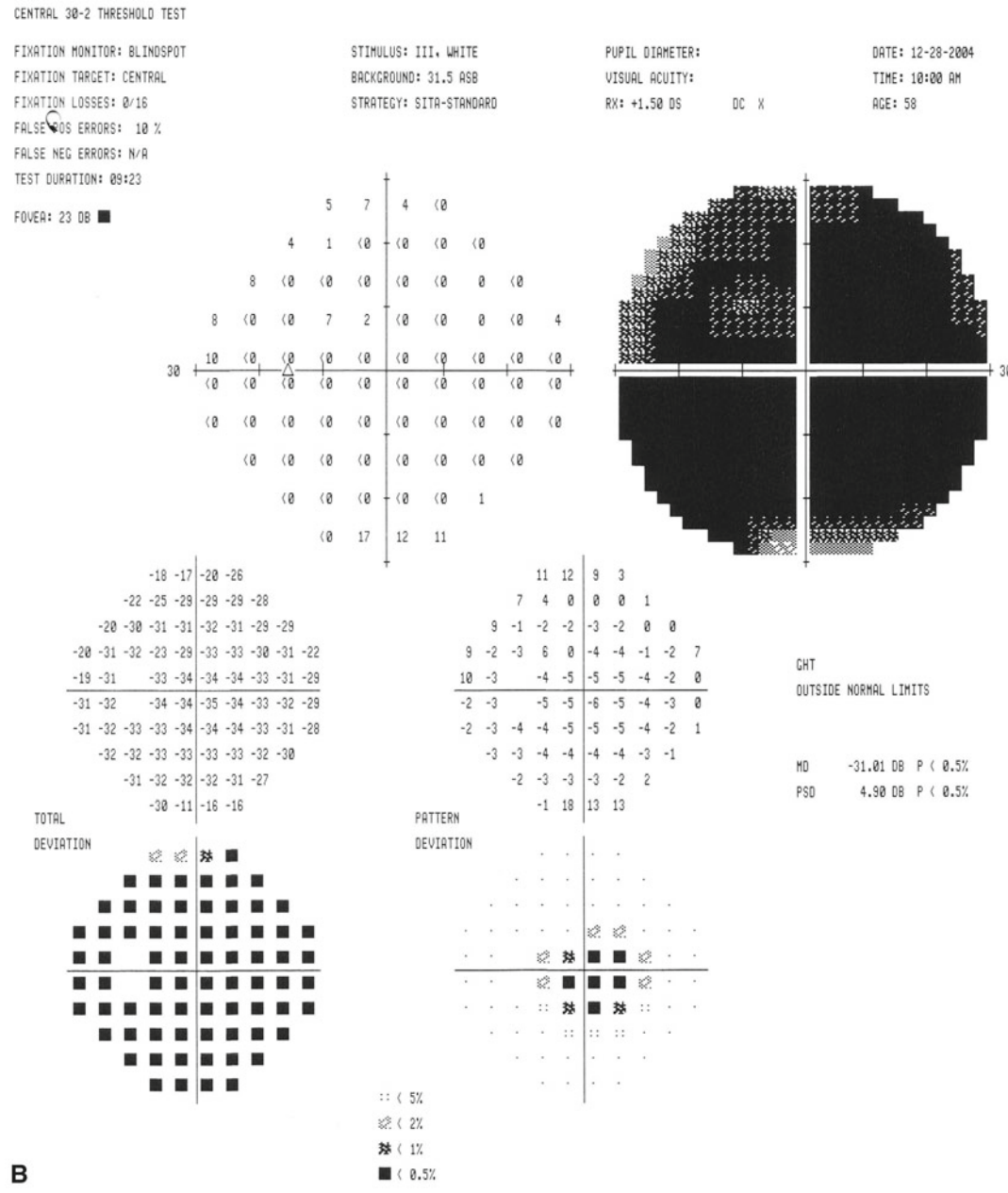
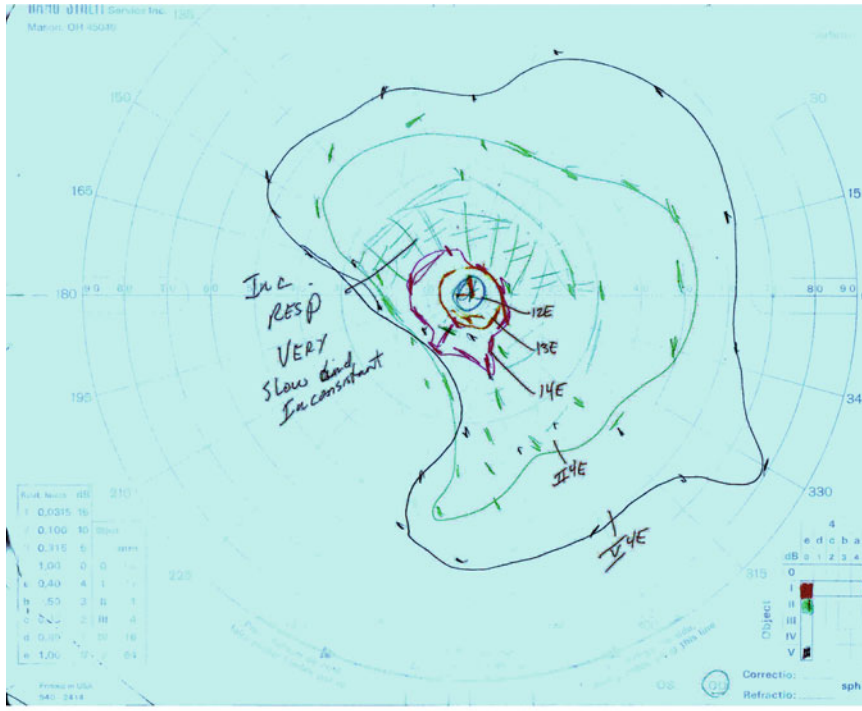
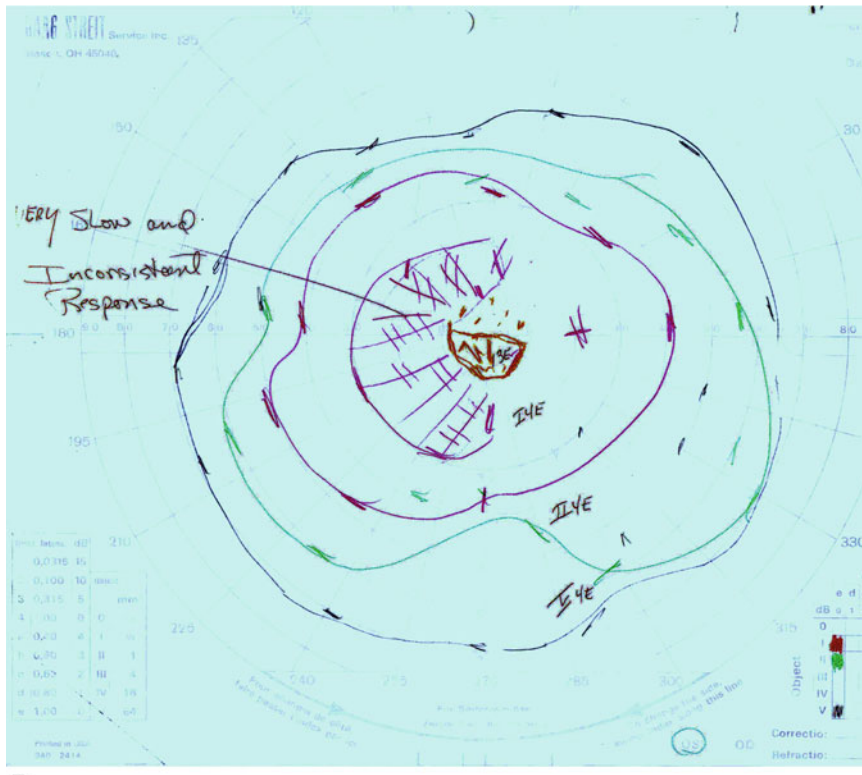


Fig. 15.3 (continued)

and 15.5). MRI brain/orbits with gadolinium demonstrated multiple hyperintense lesions throughout the brain with no evidence of optic nerve enhancement. Laboratory evaluation was negative for CAR antibody, FTA, and RPR. The patient was treated with prednisone 100 mg daily and a subsequent taper as the inflammation improved. Two months after initial presentation,

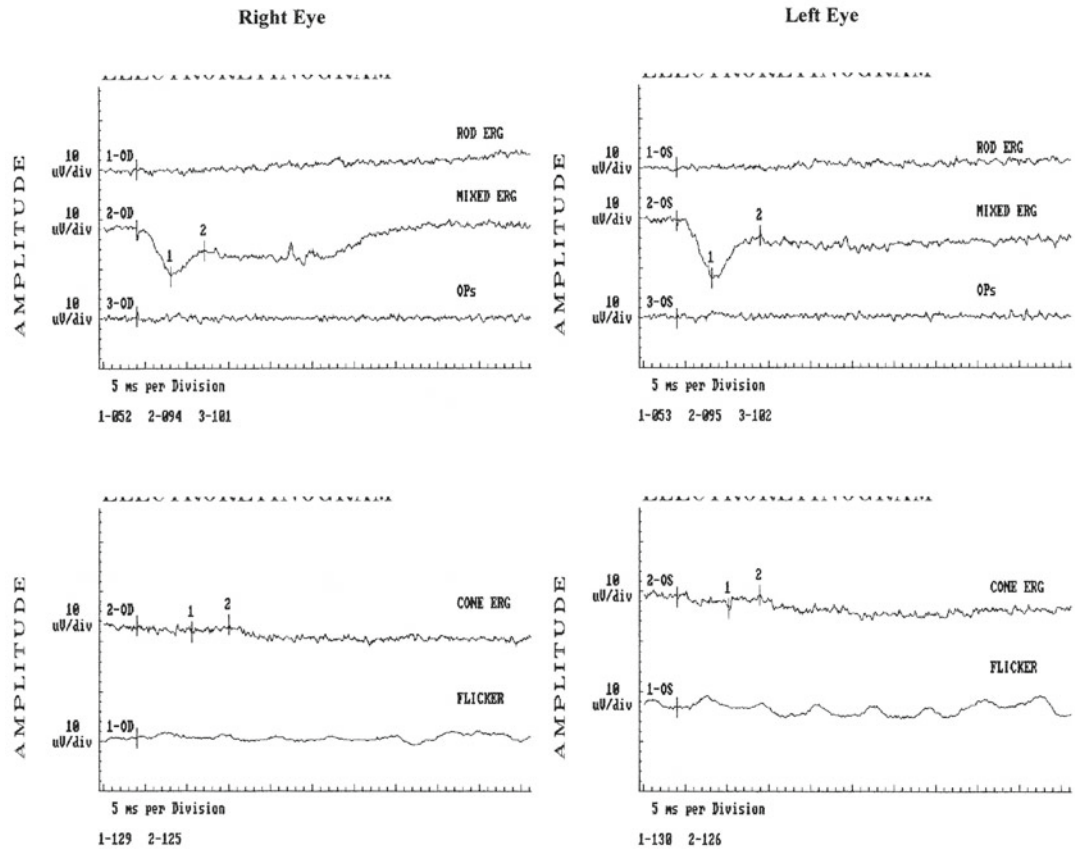


A



B

Fig. 15.4 CAR case 1: Goldmann visual fields (**a**) OD and (**b**) OS demonstrate field constriction and depression in both eyes, right eye greater than left eye



		Amplitude (uV)		Timing (ms)	
		Right eye	Left eye	Right eye	Left eye
ROD ERG:	b-wave	--	--	--	--
MIXED ERG:	b-wave	25.5	42.4	40.5	50.0
	a-wave	47.7	59.5	20.5	21.0
OSCILLATORY POTENTIALS:					
CONE ERG:	b-wave	3.7	9.3	51.0	51.0
	a-wave	17.9	18.9	22.5	18.0
	30 Hz flicker	4.9	11.5	38.6	37.8

Fig. 15.5 CAR case 1: full-field ERG demonstrates that rod ERG was not detectable; mixed cone and rod ERG was reduced in amplitude and b/a <1; and cone ERG was severely reduced in amplitude and prolonged. Overall, the full-field ERG and VEP responses were markedly impaired

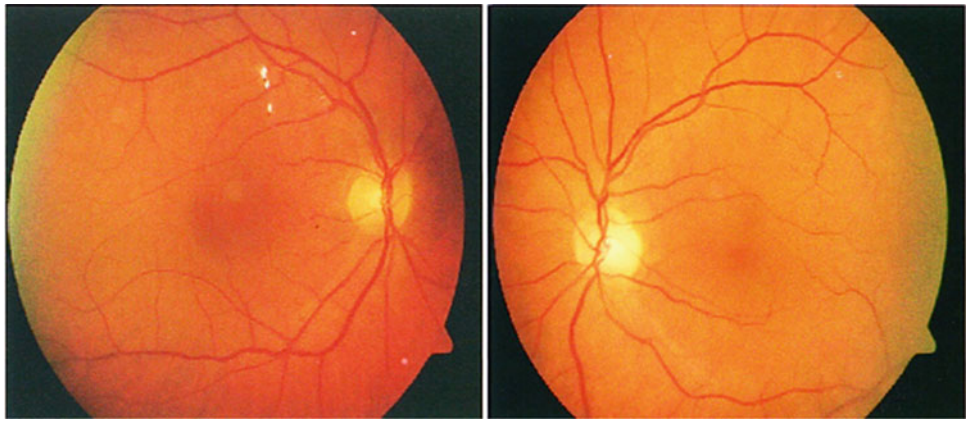


Fig. 15.6 CAR case 2: fundus photos of OD and OS demonstrate clear media, C/D 0.3 OU with no evidence of disk edema, and a blunted foveal reflex OU

the patient was symptomatic with a neck mass. Biopsy results and a subsequent total body scan demonstrated metastatic esthesioneuroblastoma. Antibody determinations were not available, but it was concluded that the ocular inflammation was a paraneoplastic retinopathy.

CAR Case 2: CAR Associated with Metastatic Breast Cancer

A 66-year-old female with a history of metastatic breast cancer treated with prior chemotherapy complained of progressively decreasing vision in both eyes for 6–8 months. Best corrected visual acuity is 20/60 OD and 20/70 OS. Clinical examination demonstrated no evidence of afferent pupillary defect, and there were full extraocular movements and confrontational field testing. There was no evidence of anterior chamber or vitreous cell, and no disk edema. Cystoid macular edema was present in both eyes (Fig. 15.6), and there were peripheral reticular pigmentary changes in the retina (not shown). Goldmann visual field testing revealed constriction of the I-4e and II-4e isopters that was asymmetric (Fig. 15.7a, b). Fluorescein angiography did not reveal retinovascular leakage although the optic nerves were mildly hyperfluorescent (Fig. 15.8). There were mild ERG changes (Fig. 15.9). MRI brain/orbits with contrast demonstrated no evidence of cerebral metastasis or orbital involvement. Laboratory testing demonstrated positive anti-enolase antibody and a negative CAR antibody. The patient was started on Taxol chemotherapy by her oncologist.

CAR Case 3: Paraneoplastic Optic Neuritis and Retinitis Associated with Small Cell Lung Cancer

A 72-year-old male with a history of testicular and epididymal mesenchymoma and abdominal sarcoma treated with surgical resection presented with progressively decreasing vision in both eyes for 4 months [9]. Best corrected visual acuity was 20/200 OD and 20/400 OS. Evaluation indicated no afferent pupillary defect, and color plates were 5/15 OD and 8/15 OS. Goldmann visual fields had central depression as well as constriction in both eyes, OS greater than OD. Clinical examination demonstrated no anterior chamber inflammation, +1 vitreous cells OU, and marked disk edema in both eyes with bullous fluid extending to the macula (Fig. 15.10). Fluorescein angiography showed optic nerve leakage (Fig. 15.11). ERG was markedly abnormal

(Fig. 15.12). The patient was evaluated for malignancy, including CNS lymphoma. Lumbar punctures revealed increased protein, and negative cryptococcal antigen and VDRL. Cytology from the diagnostic vitrectomy OD showed that the majority of cells were T cells with a predominance of CD4-positive T cells, a minor heterogeneous B cell population with a normal kappa to lambda ratio. Chest CT demonstrated mediastinal adenopathy with a left hilar mass, which upon biopsy was consistent with small cell lung cancer. Antibody testing showed a positive CRMP-5-IgG and negative CAR antibody. The patient was treated with systemic chemotherapy, radiation, and oral prednisone with improvement in his ocular condition (Figs. 15.13a, b and 15.14a, b).

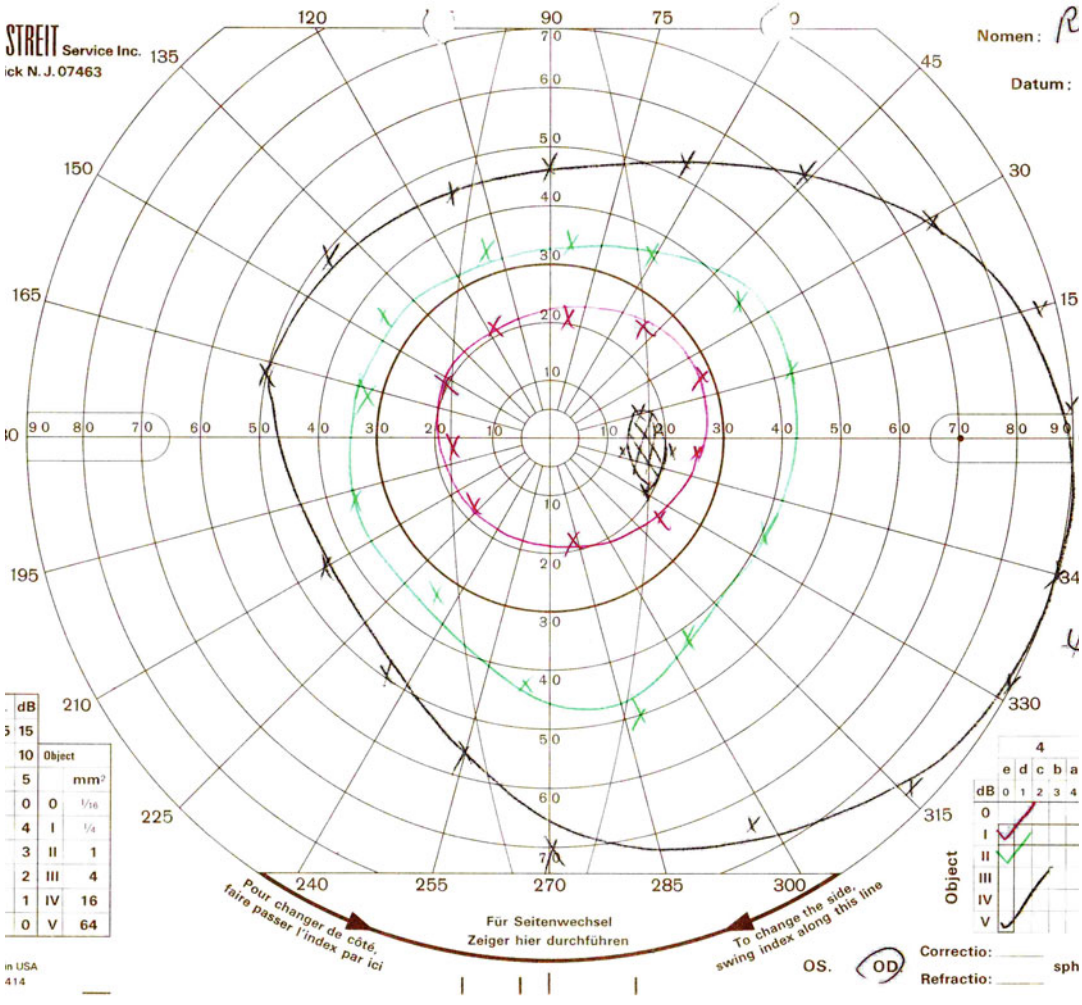
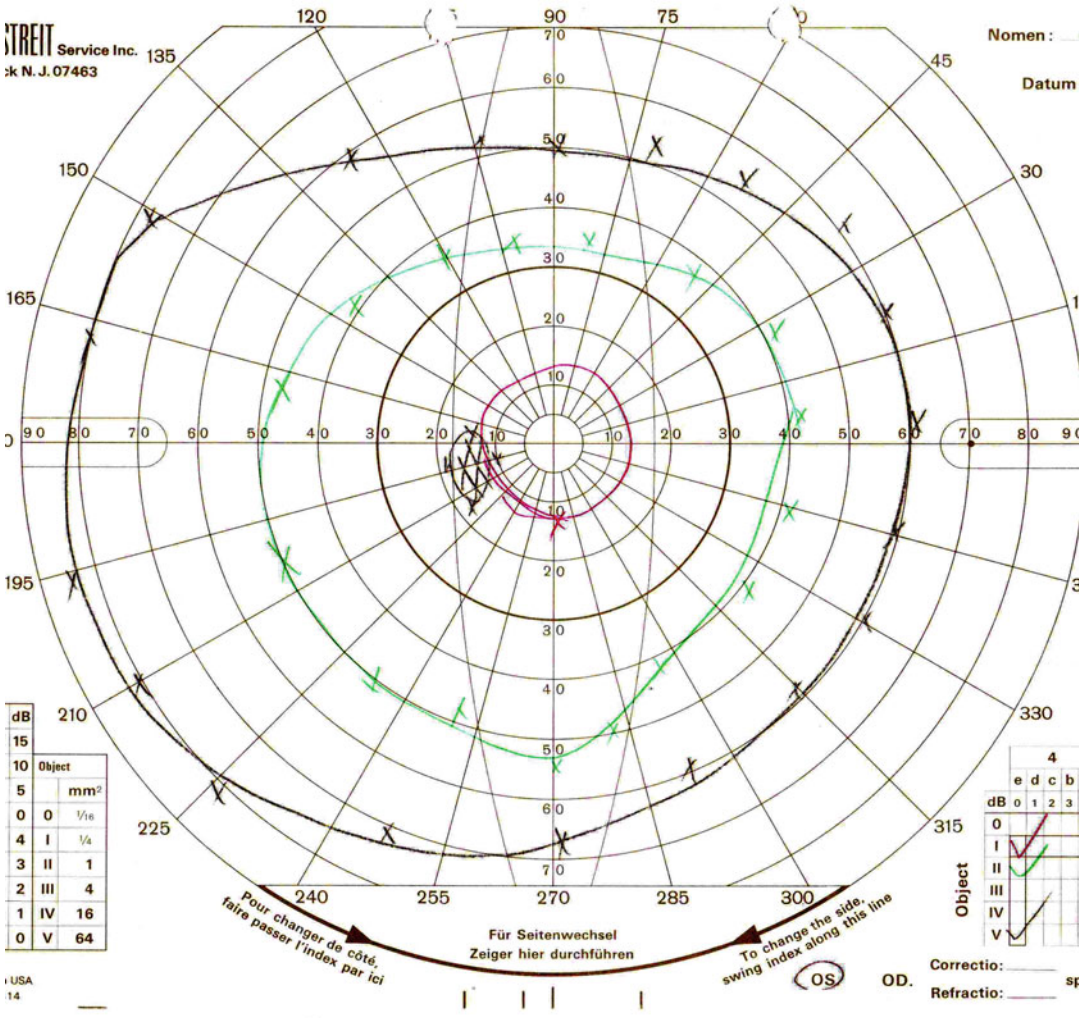


Fig. 15.7 CAR case 2: Goldmann visual fields (**a**) OD and (**b**) OS demonstrate a full field to the largest isopter with symmetric constriction of the smaller isopters. There was no evidence of peripheral field constriction or ring scotomas



B

Fig. 15.7 (continued)

Paraneoplastic Retinopathy: Melanoma-Associated Retinopathy (MAR)

Melanoma-associated retinopathy (MAR) is a form of paraneoplastic retinopathy that has been described in patients with cutaneous malignant melanoma. MAR commonly presents after the melanoma is diagnosed, often at the stage of metastases. MAR has been reported to occur in higher frequency in men than women [4]. Berson et al. in 1988 initially classified MAR as a paraneoplastic retinopathy in a patient with both visual loss and the diagnosis of metastatic melanoma [28].

The pathogenesis theory of MAR is based on molecular mimicry: tumor cells and retinal bipolar cells share epitopes [29, 30]. The tumor's retina-like antigens sensitize the immune system. The immune system, in turn, recognizes certain portions of the retina as foreign. The specific antigen responsible for MAR has not been determined, but analysis of previous cases has shown autoantibodies to bipolar cells, Muller cells, and membrane-associated proteins within the retina

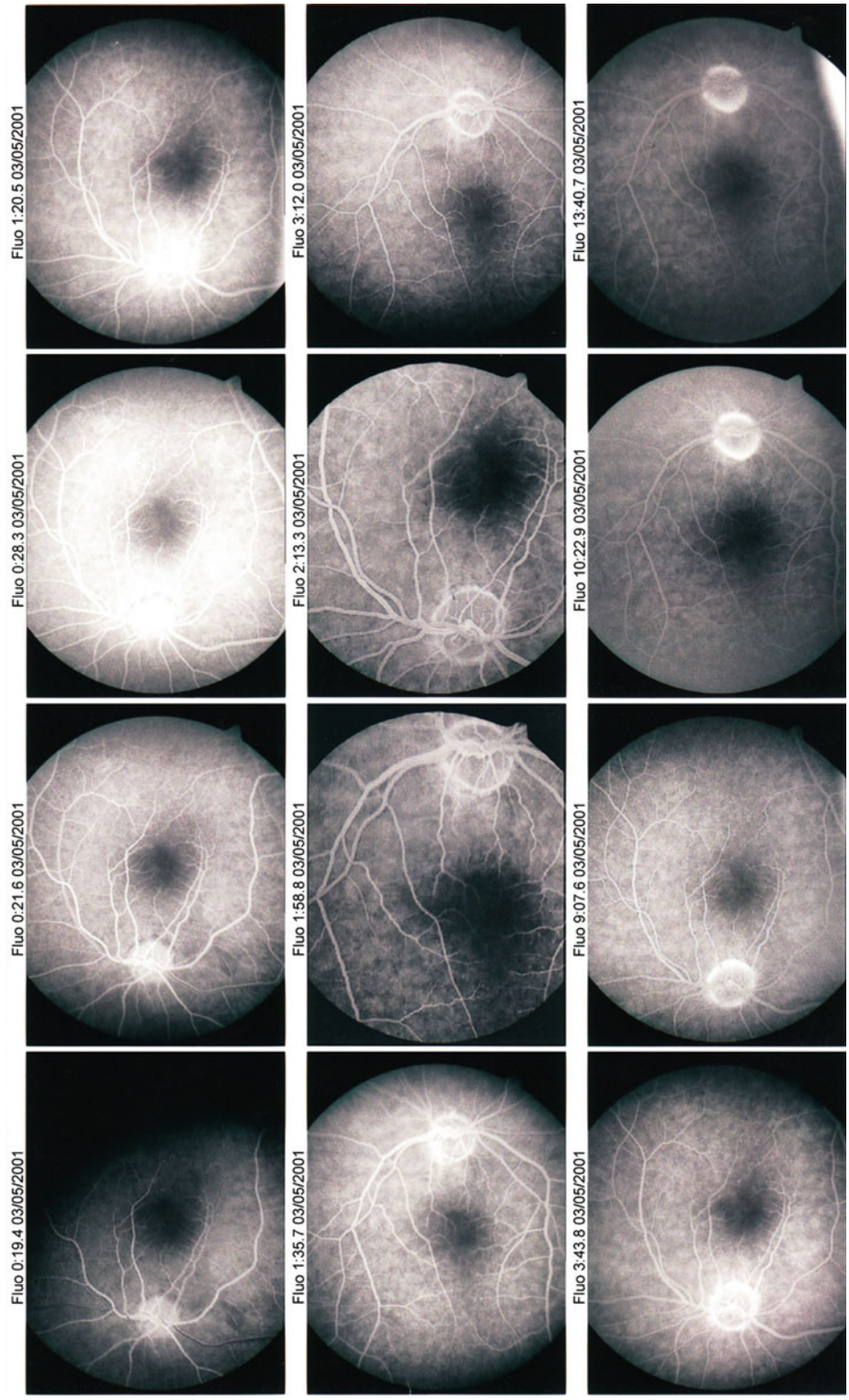
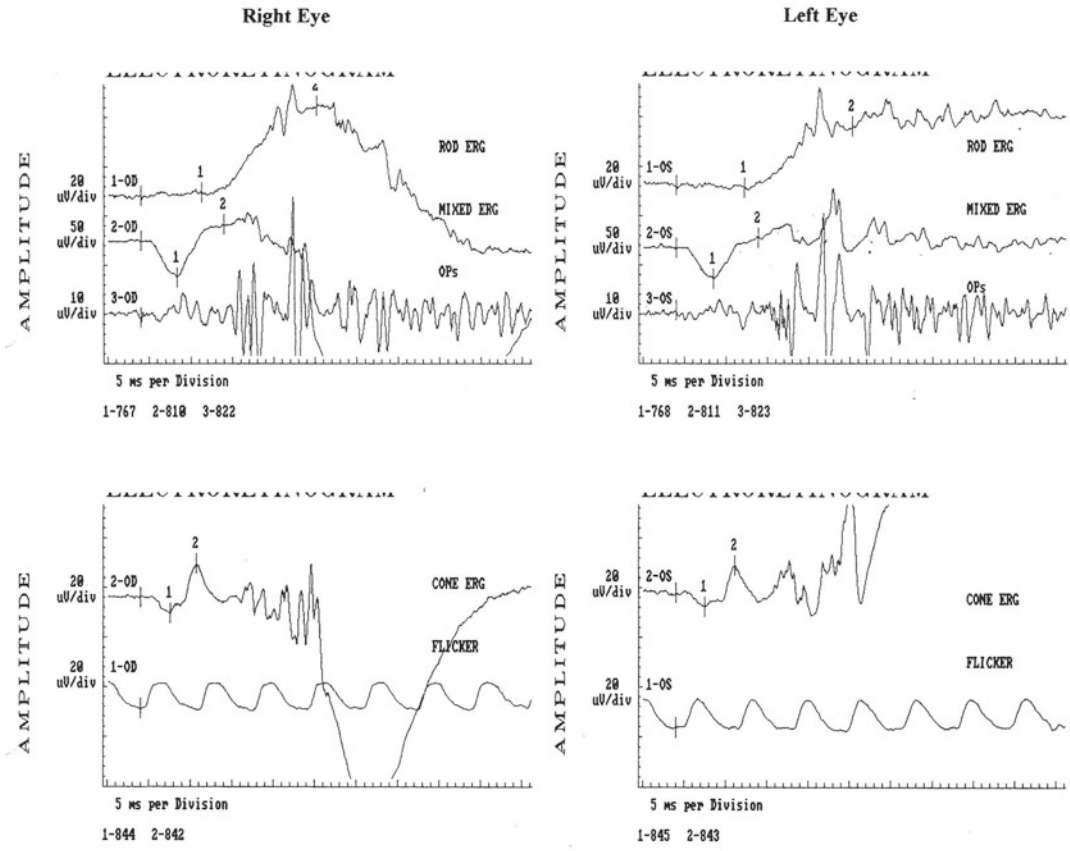


Fig. 15.8 CAR case 2: fluorescein angiography demonstrates no leakage of dye at the macula, optic nerves, or vasculature, despite clinical cystoid macular edema. Cystoid macular edema is an infrequent finding in CAR



		Amplitude (uV)		Timing (ms)	
		Right eye	Left eye	Right eye	Left eye
ROD ERG:	b-wave	175.3	124	106.0	106.5
MIXED ERG:	b-wave	274	212.4	50.0	49.5
	a-wave	183.9	158.3	22.0	22.5
OSCILLARY POTENTIALS:					
CONE ERG:	b-wave	102.5	85.4	33.5	35.5
	a-wave	34.7	32.2	18.0	17.5
	30 Hz flicker	54.4	59.4	33.3	35.2

Fig. 15.9 CAR case 3: rod ERG is slightly below the lower end of normal in amplitude and prolonged; mixed cone and rod ERG shows a-reduced and b-waves normal in amplitude; and the cone ERG is normal in amplitude and implicit time. Overall, the ERG was abnormal in each eye with relatively mild reduced rod dysfunction compared to cone responses

[30–35]. The most common hypothesis is that autoantibodies react with rod bipolar cells and their dendrites in the outer plexiform layer of the retina and cause failure of neural transmission from rods to the inner retina [4].

In the setting of clinical features, patients may present with photopsias including shimmering or flickering lights, night blindness, and peripheral visual field loss [4]. MAR patients will often have near normal visual acuity, color

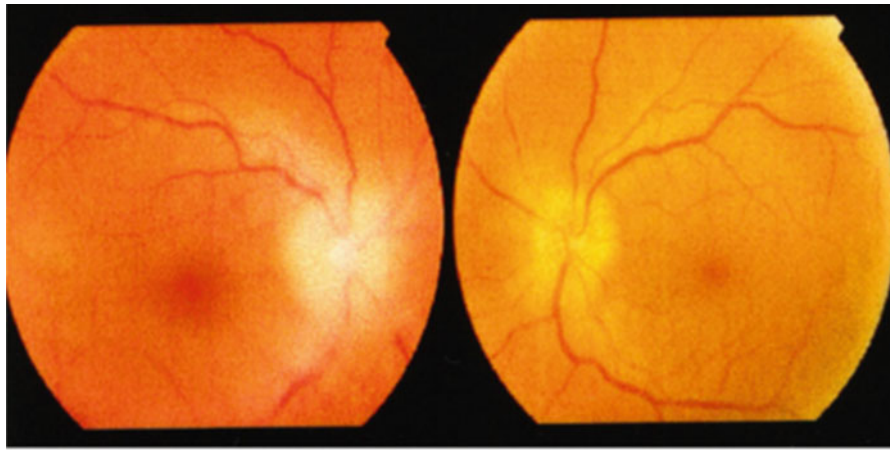


Fig. 15.10 CAR case 3: Fundus photos OD and OS demonstrate hazy media secondary to vitritis, disk edema OU, and a blunted foveal reflex secondary to macular edema

vision, and central visual field [4]. In contrast to CAR, only rods are affected and cones are spared. The most common fundus finding is that of a normal retina. Approximately 25–35% of patients will have vitreous cell, vessel attenuation, retinal pigment epithelium (RPE) changes, or optic nerve pallor [30].

The histopathologic result may be the destruction of normal retinal architecture, especially the inner retinal layers [36, 37]. Specifically, there may be reduction of bipolar neurons in the inner nuclear layer with normal photoreceptor cells in the outer nuclear layer and possible evidence of ganglion cell transsynaptic atrophy [4].

The diagnosis of MAR is based upon a positive history of malignant melanoma and the demonstration of patient IgG autoantibodies reacting with human donor rod bipolar cells on immunofluorescent stains. However, anti-bipolar cell antibodies are not specific to MAR. Typical ERG findings include a negative scotopic waveform with a markedly reduced or absent dark adapted b wave, indicating bipolar and Muller cell dysfunction, and sparing of the a wave [4].

Recently, treatment has been reported to involve reduction of tumor load by surgery or radiation to allow adjuvant immunotherapy (intravenous immunoglobulin [IVIg], plasmapheresis, or systemic corticosteroids) to be more effective [30]. Unfortunately, the vast majority of patients have metastatic disease at diagnosis [30]. Keltner et al. in 2001 described therapeutic outcomes in 11 MAR patients. Cytoreductive surgery was reported to improve visual acuity and visual field in one patient and the color vision and visual field in another [4, 30]. Also, IVIg alone improved the visual acuity in one patient, and both IV methylprednisolone and plasmapheresis improved the visual acuity and visual field in another patient [4, 30]. In other reports, IVIg and cytoreductive surgery were effective in improving visual symptoms, visual field, and color vision in one patient [38] and visual field in another patient [4, 39]. The reported cases of MAR in the literature indicate that steroids alone may not likely improve vision. In only 3 out of 64 MAR patients, steroids decreased vitreous haze and improve retinal phlebitis [4, 29, 40]. However, combination therapy with plasmapheresis, oral prednisone, azathioprine, and gabapentin together improved the visual fields and ERG in one patient [4]. Similar to CAR, ineffective treatments may also be the result of irreversible damage to retinal cells and raise the question of whether visual loss can be prevented with treatment prior to structural damage. Overall, the long-term stabilization of visual outcome and prognosis for MAR is unknown at this time and will require longer follow-up data in the reported literature.

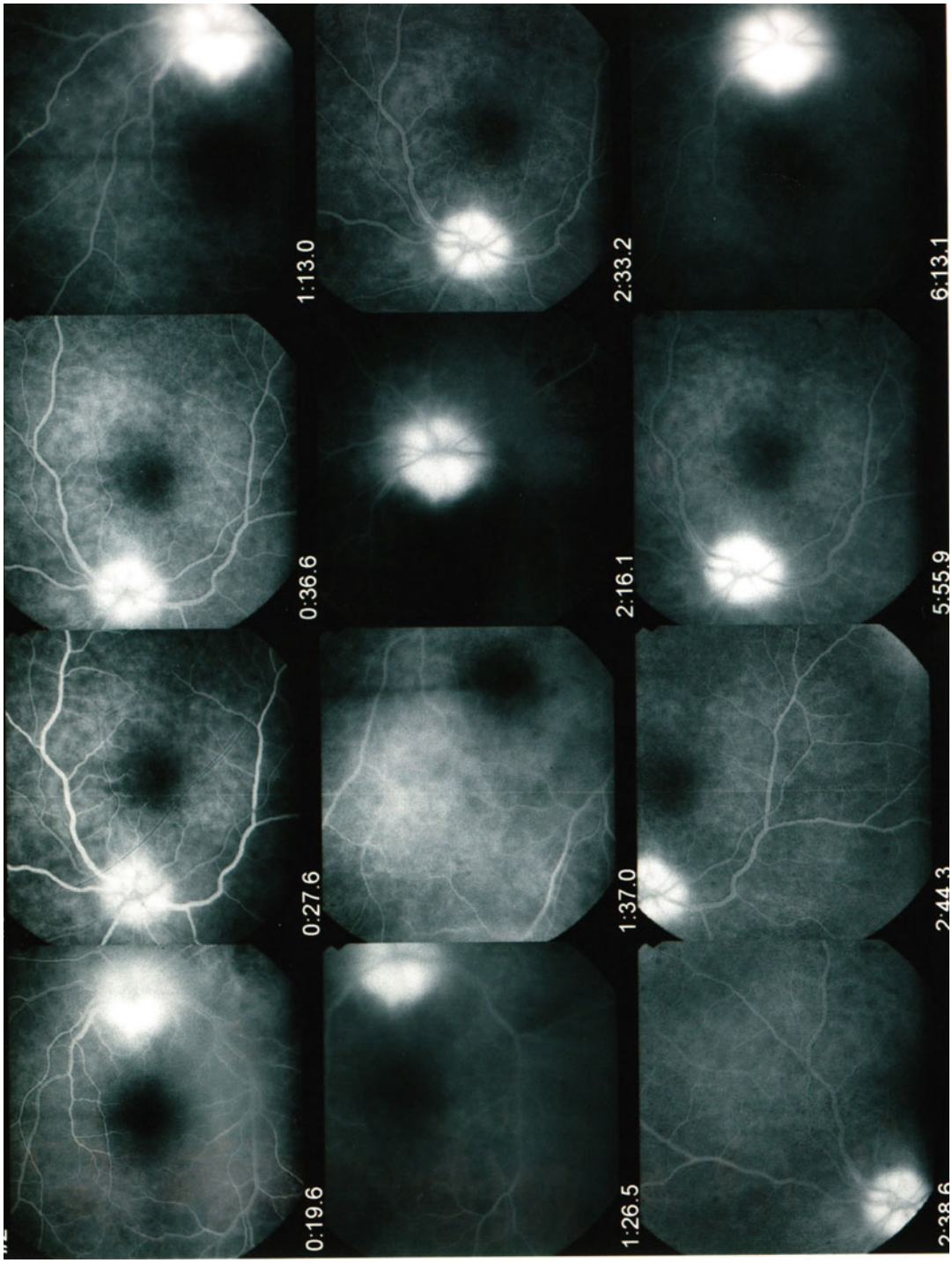
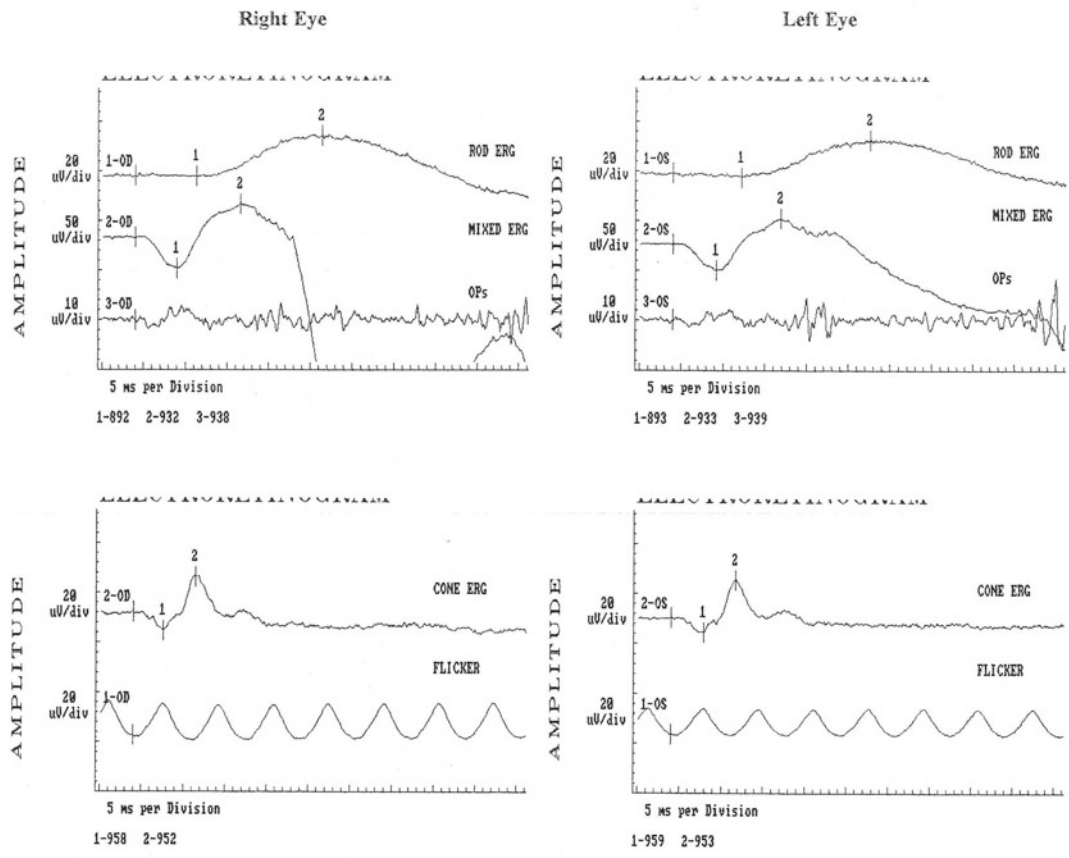


Fig. 15.11 CAR case 3: Fluorescein angiography at the initial visit demonstrates leakage from the optic nerves, OD greater than OS



		Amplitude (uV)		Timing (ms)	
		Right eye	Left eye	Right eye	Left eye
ROD ERG:	b-wave	81.5	77.9	112.0	118
MIXED ERG:	b-wave	327.1	263	63.0	64.5
	a-wave	159.1	133.6	25.0	26.0
OSCILLATORY POTENTIALS:		41.2	53		
CONE ERG:	b-wave	110.1	107.4	37.0	38.5
	a-wave	35.7	29.4	18.0	19.5
	30 Hz flicker	73.6	56.0	37.9	38.8

Fig. 15.12 CAR case 3: Rod ERG is reduced in amplitude with prolonged implicit time; mixed cone and rod ERG shows that a and b waves are at lower end of normal in amplitude but prolonged; and cone ERG is normal in amplitude but markedly prolonged. Overall, full-field ERGs showed rod and cone dysfunction–based amplitudes with prolonged response for both rods and cones

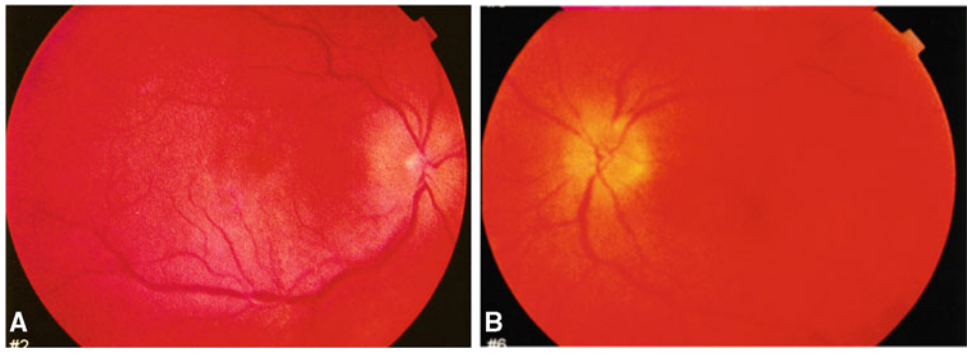


Fig. 15.13 CAR case 3: Fundus photos (**a**) OD and (**b**) OS 1 month after initiating systemic chemotherapy and radiation for small cell lung cancer, which demonstrated improved disk edema OU. Visual acuity improved to 20/50 OD and 20/80 OS

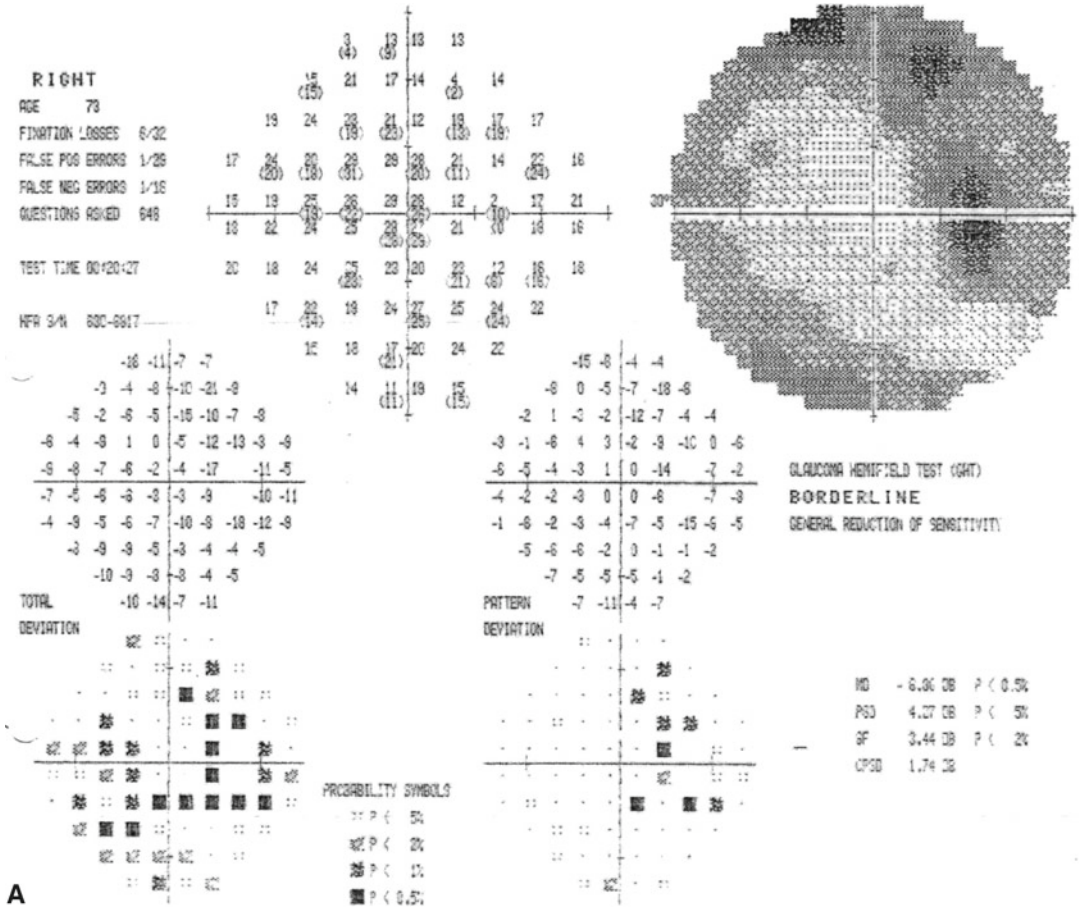


Fig. 15.14 CAR case 3: (**a**) HVF 30–2 OD and (**b**) OS 1 month after initiating systemic chemotherapy and radiation demonstrate improved constriction OU. Visual acuity improved to 20/50 OD and 20/80 OS

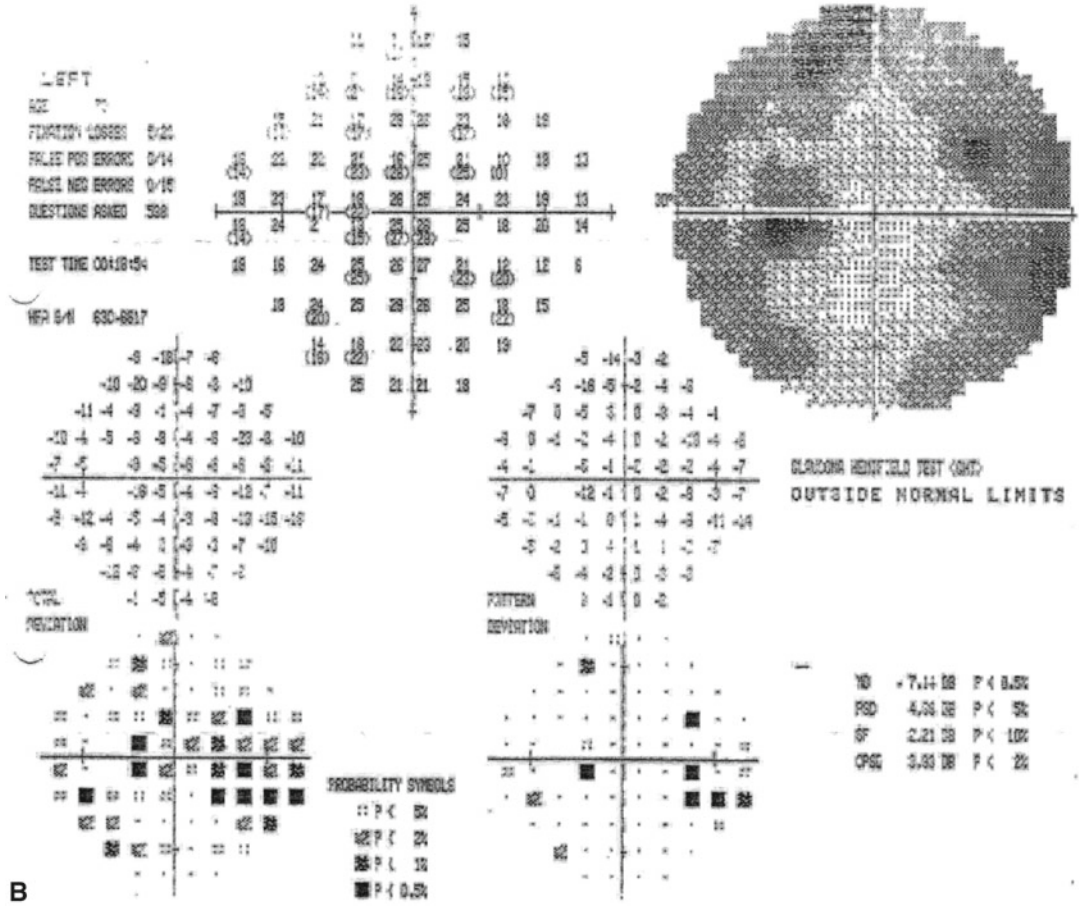


Fig. 15.14 (continued)

MAR Case

A 57-year-old Hispanic male presented with bilateral nyctalopia, blurred vision, and occasional flashes for the past month. His history was significant for excision of a small melanoma from his right heel approximately 3 years previously. He received a brief course of interferon therapy following the melanoma excisional biopsy, which was completed approximately 2½ years prior to presentation. Initial and all subsequent metastatic workups (most recently 2 years prior to presentation) were negative. The patient's family members had no heritable ocular diseases. He gave no history of tobacco, alcohol, or street drug use.

On examination, best corrected visual acuity was 20/40 OD and 20/25 OS. The anterior chambers were quiet, and intraocular pressure was 16 OU. There were trace vitreous cells. A retinal pigment epithelial detachment (RPED) was present superior to the fovea in the right macula, and there were some minor pigmentary changes in the left macula (Fig. 15.15a, b). There were myelinated nerve fibers OD and an area of retinal whitening in the inferonasal periphery (Fig. 15.15c, d)

On fluorescein angiography, the most striking aspect of the angiogram was the late staining of the optic disk and vasculature, right eye greater than left eye (Fig. 15.16a–d). Pigment epithelial

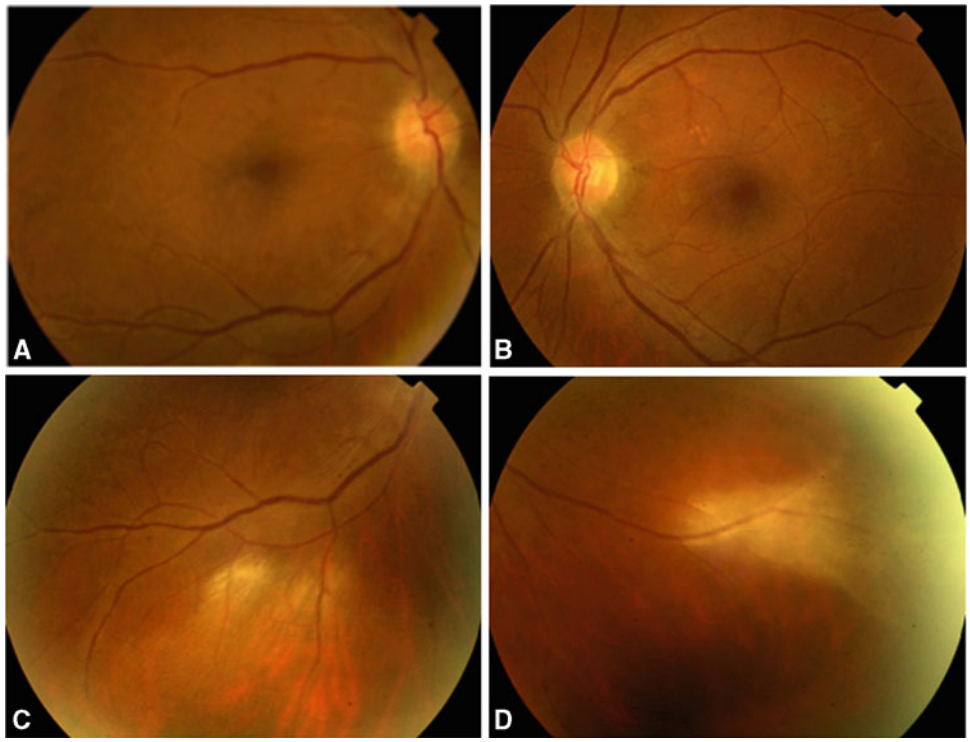


Fig. 15.15 MAR case. (**a**) Fundus photo OD shows elevated lesion superior to fixation in the right macula suggestive of a pigment epithelial detachment. (**b**) Fundus photo OS shows flat pigmentary alterations in the left macula. (**c**) Myelinated nerve fibers are present below the inferior arcade OD. (**d**) There is an area of superficial retinal whitening OD approximately one disk area in size inferonasally. This *whitening* appeared more intense around the arterioles and venules

defects and an RPED were confirmed. Humphrey and Goldmann visual fields showed generalized severe reduction of sensitivity to the size III stimulus and constriction of the peripheral fields (Fig. 15.17). An ERG showed loss of the scotopic B wave consistent with his complaints of nyctalopia and as previously reported in MAR [41]. Testing for autoantibodies directed against retina was performed at the University of California at Davis.

The differential diagnosis of low-grade retinal vasculitis of indolent course associated with nyctalopia and mild decreased visual acuity with constricted fields was quite broad and included infectious, inflammatory, pharmacologic, neoplastic, and idiopathic causes. The history of interferon treatment raised the possibility of interferon retinopathy with retinal ischemia, but these findings usually resolve within 9–12 months after cessation of interferon. This patient had no cotton wool spots, which are seen in almost all cases, and his last interferon dose was more than 2 years ago making interferon retinopathy highly unlikely.

Given the patient's history of cutaneous melanoma, the leading diagnostic consideration was melanoma-associated retinopathy. This paraneoplastic syndrome commonly presents with nyctalopia. However, there is only one previously reported case of melanoma-associated retinopathy presenting with vasculitis [40].

Laboratory studies were performed and demonstrated normal values for the complete blood count, basic metabolic panel, ANA, ANCA, ACE, ESR and RPR. A chest radiograph revealed mild flattening of the diaphragms but no hilar lymphadenopathy or masses.

Dr. Charles Thirkill at the University of California, Davis, performed serologic and immunologic testing on blood samples from this

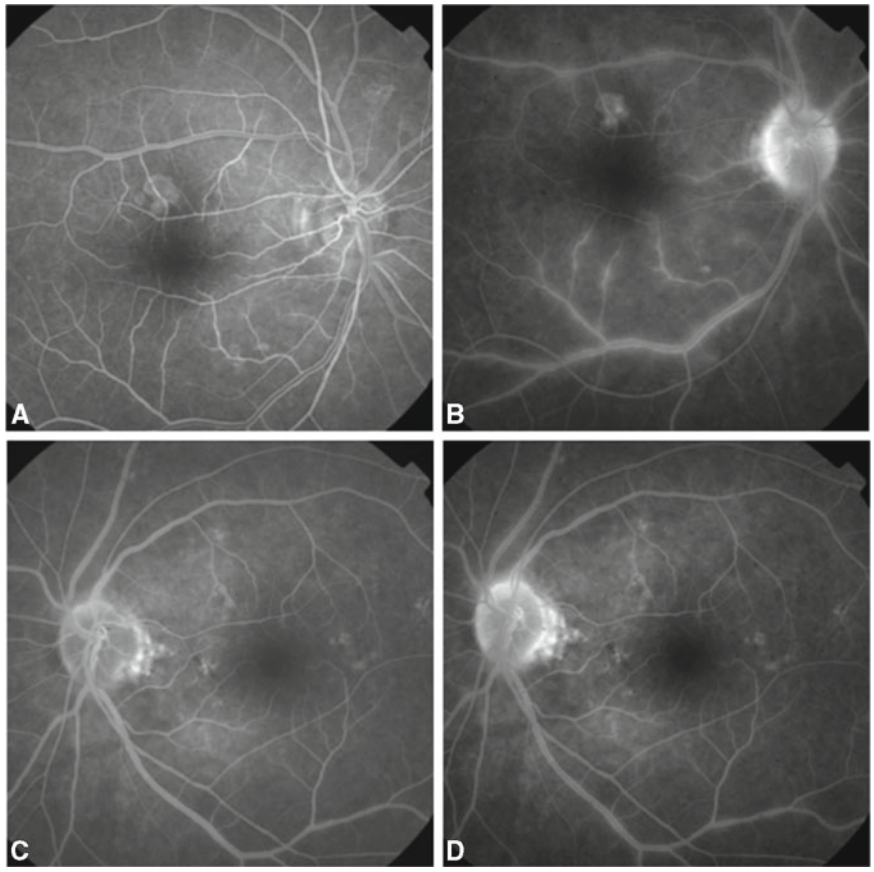


Fig. 15.16 MAR case. (**a**, **b**) Fluorescein angiography OD. (**a**) At 0:23 s, there is early hyperfluorescence in the pigment epithelial detachment, which has an atypical, irregular border and a small satellite lesion temporally. At 7:47 min, diffuse staining of the retinal veins and optic nerve is seen. (**b**) The RPED stains inhomogeneously with an irregular border. (**c**, **d**) Fluorescein angiography OS. (**c**) At 2:10 min, there are scattered areas of hyperfluorescence consistent with pigment epithelial window defects in the left peripapillary and perifoveal areas. The nerve and venules show early staining. (**d**) At 7:30 min, there is an increase in the mild staining of the proximal venules and the optic nerve

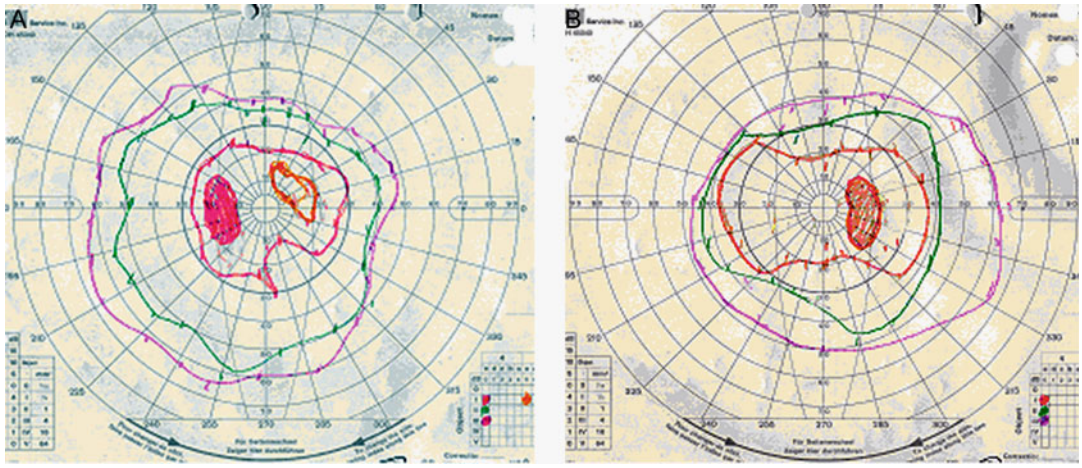


Fig. 15.17 MAR case. (**a**) Goldmann visual fields OD and (**b**) OS revealed generalized constriction

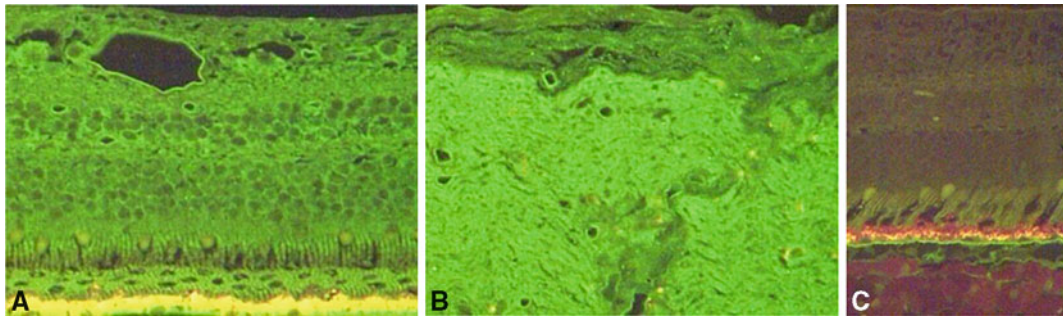


Fig. 15.18 MAR case. (**a**) The patient's serum diffusely stained all layers of rhesus monkey retina and vasculature. (**b**) The patient's serum also diffusely stained optic nerve stroma. In other reported cases of MAR, staining has been confined to bipolar cells. (**c**) Control human serum demonstrates a lack of staining of monkey retina (Courtesy of Dr. Charles Thirkill, University of California at Davis)

patient. Western blot with bovine retina extract revealed diffuse abnormal activity. Indirect immunohistochemistry revealed abnormal antibody activity upon rhesus monkey retina and optic nerve. FITC-conjugated rabbit anti-human gamma globulins indicated that human antibody had bound all layers of the neurosensory retina, vasculature, and optic nerve stroma (Fig. 15.18a, b). No human antibody from control patient serum bound the rhesus monkey retina (Fig. 15.18c).

Based on a presumptive diagnosis of MAR, the patient was treated with systemic corticosteroids. A metastatic workup revealed liver metastases related to melanoma. He survived for another 2 years before succumbing to his disease.

Autoimmune-Related Retinopathy and Optic Neuropathy (ARRON)

The disease spectrum of autoimmune-related retinopathy and optic neuropathy (ARRON) encompasses cases of retinal and/or optic nerve involvement and was classified by Keltner et al. in 2002 [30, 42]. ARRON is characterized by visual loss and often the presence of antibodies that are reactive with the optic nerve and/or retina. ARRON has been reported to be more common in women than men (2:1), and the average age is 50 years (range 37–75 years) [42–44]. The majority of ARRON patients have associated systemic immunologic diseases such as systemic lupus erythematosus, rheumatoid arthritis, thyroid disease, celiac sprue, Sjogren's disease, psoriatic arthritis, and idiopathic thrombocytopenic purpura [30, 42, 45].

The pathophysiology of ARRON syndrome has not been fully established. Autoantibodies against a 22-kDa antigen, a 23-kDa antigen (recoverin), Muller cells, a 35-kDa antigen, and a 47-kDa antigen have all been reported in the literature [43, 44]. Specifically, anti-recoverin antibody has been described to stain photoreceptors, and anti-47-kDa antibodies stain ganglion cells, bipolar cells, and Muller cells [43, 46]. Western blot analysis can be utilized to identify patients with ARRON syndrome, and most commonly demonstrate autoantibodies reactive with the 22-kDa neuronal antigen present in the retina and/or optic nerve [42]. In ARRON, it remains unclear whether antibodies directed against optic nerve and retina play a direct role in loss of visual function or whether antibodies are possibly the result of an epiphenomenon and are produced secondary to nonspecific breakdown of retinal and optic nerve proteins [45, 46].

ARRON syndrome may present in a similar clinical manner to CAR and MAR in the absence of an underlying malignancy. In the setting of visual function, ARRON patients will often present asymmetrically in terms of visual acuity and visual deficits [43]. The majority of ARRON cases will present with ERG abnormalities, which

are often detectable prior to the onset of visual loss and are similar to findings in CAR [45]. Mizener et al. in 1997 described autoimmune retinopathy in the absence of an underlying cancer [47]. They reported two patients that presented with severe monocular vision loss with photopsias, ring scotomas, abnormal ERGs, and a normal-appearing fundus [45, 47]. The sera from both patients also demonstrated antiretinal antibodies that specifically labeled the inner plexiform layer by indirect immunoperoxidase staining [45, 47]. Keltner and Thirkill in 1999 described eight patients with unexplained visual loss [46]. Seven of these cases were determined to have ARRON syndrome, and one of the eight had MAR [46]. Autoantibody reactions to the retina and optic nerve were detected in each case, including a common antibody reaction with the 22-kDa neuronal antigen [45, 46]. In 2002, Keltner and Thirkill evaluated 12 ARRON patients [42]. The described clinical findings included 11 of 12 who had optic nerve atrophy and 8 of 12 who had nonspecific retinal changes except for blood vessel attenuation in three patients [42, 45]. ERG abnormalities were present in ten patients [42]. Furthermore, there was no underlying malignancy in any of these patients, and systemic immunologic disease was present in 8 out of 12 patients [42]. Additional clinical findings included the presence of fine vitreous cells, and the visual fields displayed diffuse loss or constriction [42].

Suggestive diagnostic criteria for ARRON syndrome were described by Oyama et al. in 2009 and include four of the following features: visual loss as demonstrated either by visual acuity or by visual field examination, evidence of optic nerve or retinal abnormalities, no evidence of malignancy after extensive evaluation, and no identifiable cause for optic neuropathy and/or retinopathy [43]. Also, additional diagnostic evidence can include the presence of serum antibodies against retina and or optic nerve [43]. Screening recommendations for evaluation for an underlying malignancy can include dermatologic skin survey, colonoscopy, standard prostate screening, gynecologic examination, mammography, lumbar puncture, whole body imaging, and serum testing for recoverin and 62-kDa neuronal antigen called collapsin response mediator protein-5 (CRMP-5) [43]. The differential diagnosis for ARRON, therefore, includes similar clinical entities discussed earlier with the paraneoplastic retinopathies.

Several treatments for ARRON have been reported in the literature with variable success. The primary approach is often based upon treatment of any underlying systemic disorders. The goal of treatment for ARRON syndrome consists of suppressing the immune response [45]. Oral or intravenous corticosteroids are typically used as first-line therapy [45]. Depending on the response to corticosteroid treatment, cyclophosphamide, methotrexate, IVIg, and plasma exchange (PE) have been used singly or in combination as the next line of therapy [45]. Specifically, 70% of ARRON patients have been reported to require combination therapy [42]. In 2008, Barret et al. described a case of an ARRON patient with declining visual acuity, visual field, and color vision despite multiple treatment modalities including prednisone, methylprednisolone, IVIg, azathioprine, and methotrexate [45]. In this case, there was a successful response to plasma exchange (PE) followed by intravenous immunoglobulin (IVIg) and later PE maintenance therapy alone [45]. More recently, Oyama et al. in 2009 reported stabilization of clinical manifestations in a patient with ARRON treated with autologous hematopoietic stem cell transplantation (HSCT) [43]. In this case, the progressive hearing and visual loss was slowed by IVIG treatment; however, the peripheral symptoms continued to worsen [43]. The non-myeloablative HSCT regimen was utilized to treat this patient since an identical regimen had been used safely and with encouraging outcomes in systemic lupus erythematosus (SLE) and type I diabetes mellitus [43]. In this case, the HSCT was well tolerated, and there was an improvement in symptoms and reversal of declining visual fields and acuity [43]. There was also a reduction in the total number of antibodies after HSCT against both the retina and optic nerve [43]. As ARRON syndrome is newly described and often underdiagnosed, no treatment regimen has been proven optimal due to the

Table 15.1 Summary characteristics for autoimmune retinopathy and paraneoplastic syndromes

Conditions	Systemic associations	Clinical presentation	ERG findings	Antibody detection
CAR	Small cell lung, gynecologic, breast cancer (most common) [4]	Subacute, bilateral visual loss; entoptic symptoms; manifestations of rod and cone dysfunction; normal fundus early in disease course [1]	Abnormal scotopic and photopic response; a and b waves may both be flat	23, 46 (most common), 45, 60, 65, 44, 43, 63 kDa, TULP-1, PNR, CRMP-5-IgG [4]
MAR	Cutaneous malignant melanoma	Photopsias, near normal visual acuity, normal fundus (most common) [4]; symptoms usually present when melanoma is already diagnosed	Abnormal scotopic response with markedly reduced or absent dark adapted b wave	Autoantibodies to rod bipolar cells and dendrites in the outer plexiform layer [4]
ARRON	Systemic immunologic diseases (SLE, RA, ITP, psoriatic arthritis, thyroid disease, celiac sprue, Sjogren's syndrome) [30, 42, 45]	Similar to CAR and MAR in absence of malignancy; asymmetric visual acuity and visual field deficits [43]	Abnormal scotopic and photopic patterns (similar to CAR)	22 (most common), 23, 35, and 47 kDa [43, 44]

limited number of cases. Further studies will be needed to determine and evaluate for an effective long-term treatment approach.

Pearls

See Table 15.1.

- Autoimmune retinopathies and paraneoplastic retinopathies are rare ocular conditions with diverse and often subtle clinical and immunological features that require a high index of clinical suspicion.
- CAR is most frequently associated with small cell carcinoma of the lung, and antibodies are directed against both rods and cones resulting in ERG abnormalities in the majority of cases. Antibodies directed toward recoverin, a 23-kDa retinal protein, and 46-kDa retinal enolase are most commonly identified.
- The key diagnostic features with MAR are a history of cutaneous malignant melanoma, and a negative ERG pattern with antibodies being directed most commonly against rod bipolar cells. In both CAR and MAR syndromes, the fundus can appear normal in the early stage of the disease.
- ARRON typically presents with asymmetric visual loss, and antibodies are directed against the retina and/or optic nerve without the presence of an underlying malignancy. ERG findings may be similar to CAR. Autoantibodies reactive with the 22-kDa neuronal antigen are most commonly demonstrated.
- Many retinal antibodies involved in these autoimmune retinopathies likely remain to be identified.
- Future considerations are for standardization of assays to measure the presence and titers of antiretinal antibodies in order to enhance the clinical value of antibody testing for these conditions [48].

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