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REVIEW

Autoimmune retinopathy: A review and summary

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Abstract Three main forms of autoimmune retinopathy (AIR) have been identified over the last 15 years: cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), and nonneoplastic autoimmune retinopathy (npAIR). In this chapter, the term AIR will be used to encompass all three disorders where there is commonality to their features. Complicating the issue is that AIR can be a secondary complication of other conditions such as retinitis pigmentosa, ocular trauma, birdshot retinopathy, acute zonal occult outer retinopathy (AZOOR), or multiple evanescent white dot syndrome (MEWDS). The many forms of AIR tend to have common clinical features despite the fact that there has been no uniform set of anti-retinal antibodies circulating in these patients. Patients tend to have a wide variance of anti-retinal antibody activity often with three to six different antibodies found on immunoblots. Patients typically present with a sudden onset of photopsia, rapid visual loss, and abnormal electroretinograms (ERGs). Most patients have a panretinal degeneration without pigment deposits.

Keywords Autoimmune disease · Autoimmune retinopathy · Cancer-associated retinopathy · Melanoma-associated retinopathy · Cystoid macular edema · AZOOR

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Three main forms of autoimmune retinopathy (AIR) have been identified over approximately the last 15 years: cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), and non-neoplastic autoimmune retinopathy (npAIR). In this chapter, the term AIR will be used to encompass all three disorders where there is commonality to their features. Complicating the issue is that AIR can be a secondary complication of other conditions such as retinitis pigmentosa, ocular trauma, birdshot retinopathy, acute zonal occult outer retinopathy (AZOOR), or multiple evanescent white dot syndrome (MEWDS). The many forms of AIR tend to have common clinical features despite the fact that there has been no uniform set of anti-retinal antibodies circulating in these patients. Patients tend to have a wide variance of anti-retinal antibody activity often with three to six different antibodies found on immunoblots.

Most AIR patients do not have a previous history of visual problems or night blindness, and develop a sudden onset of photopsias, followed by other symptoms such as night blindness, scotomata, and visual field loss. Some patients also develop diminished central vision and loss of contrast sensitivity. The presentation may be asymmetric between eyes. Initially, on examination there are frequently no discernible changes on ophthalmoscopy, but a standardized electroretinogram (ERG) will show abnormal responses. Some cases have negative waveforms, consisting of an a-wave, and a b-wave that does not return to the isoelectric point in the dark-adapted, bright-flash ERG testing modality. Kinetic visual fields are better at detecting peripheral losses or scotomata, blind spot enlargements, or pericentral losses, although some patients will have abnormalities early on static perimetry [5].

Establishing the diagnosis

Autoimmune retinopathy (AIR) currently is among the more difficult ophthalmic diagnoses to establish as there are few definitive tests, and a combination of positive diagnostic features has to be present to have confidence that the diagnosis is correct. The spectrum of autoimmune retinopathies includes the better-known paraneoplastic syndromes such as cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR), as well as retinopathies without an underlying malignancy that have similar clinical and immunological features (the non-paraneoplastic autoimmune retinopathies or npAIR).

The diagnosis of AIR is made by weighing the available above-clinical evidence, finding anti-retinal antibodies on Western blot, and is confirmed if the patient has anti-recoverin or anti-alpha enolase antibodies [14, 15, 19]. However, many patients who fit this clinical picture do not have anti-recoverin or enolase antibodies, but mixtures of other ones.

AIR typically occurs without signs of inflammation (cell or flare) in the front or back of the eye, and signs of uveitis are not a usual feature in the disorder. A caveat is that we have seen a few patients with chronic intermittent uveitis who have developed AIR later in their disease process, which is treatable with immunosuppression.

Disorders, which will be discussed in this chapter include: (1) cancer-associated retinopathy (CAR); (2) melanoma-associated retinopathy (MAR); (3) non-paraneoplastic autoimmune retinopathy (npAIR); (4) cystoid edema in retinitis pigmentosa; (5) panretinal degenerations without pigment deposits that show fast progression; and (6) selected cases of AZOOR, MEWDS, blindspot syndrome, and birdshot retinopathy.

All have autoimmune anti-retinal antibodies which appear to play a pathologic role. The main diagnostic features associated with most cases of autoimmune retinopathy are:

1. Panretinal degeneration with no or little pigment deposition
2. Fast progression by history or visual field
3. Severe electroretinographic changes. Negative waveforms are common. In earlier cases, more severe ERG changes in face of relatively normal retinas or larger visual field sizes are contributing evidence to the AIR diagnosis.
4. History of autoimmune disease in the family and/or patient
5. Multiple bands of anti-retinal antibody activity on Western blot of the patient's serum
6. Improvement of visual function on at least a 3-month trial of immunosuppression
7. History of carcinoma or melanoma in association with points 1–3
8. Cystoid macula changes in retinitis pigmentosa patients; may present as edema or a macular schisis-like process

Western immunoblots of AIR patients' serum against normal donor retinal protein extracts will typically show anti-retinal IgG bands of activity (Table 1). Demonstrated activity against the retinal protein recoverin is pathognomic for AIR and when antibodies against α-enolase, arrestin, carbonic anhydrase, TULP-1, HSP70, and PNR are present, the diagnosis is strongly supported if other features are present [1–3]. Most active cases have a minimum of three different anti-retinal antibodies on Western blot. It should be noted that a patient who has random serum anti-retinal antibodies alone does not establish the diagnosis of AIR, but when multiple easily identifiable bands are present along with the typical clinical findings, it lends support to making the diagnosis, and is an indication of an active autoimmune status of the patient.

Western blots using retinal homogenate substrate do not give specific information as to the underlying antigenic retinal protein; while a band may show at a weight of 23 kDa, it does not mean that it is identifying anti-recoverin reactivity. In screening 521 RP patients with Western blots, 51 had 23-kDa bands, but only eight of the 51 had specific immunoreactivity to recoverin protein, so there is at least one other retinal protein at 23 kDa that reacts with many patients' sera [4]. Immunoassays or proteomic identification for specifically identifying underlying antigenic retinal proteins (Table 1) need to be performed before statements can be made as to antigenic causation in any particular patient.

Cancer-associated retinopathy (CAR syndrome)

Hoyt originally noted paraneoplastic associated blindness in 1976 as a "remote effect of cancer" [6] and there were sporadic reports or paraneoplastic blindness until Thirkill, Roth, and Keltner more clearly defined the CAR syndrome

Table 1 Proteins which have been associated with autoimmune retinopathy [7, 8, 13, 19–20]

Name	Weight (kDa)
Recoverin	23
Carbonic anhydrase	30
Transducin β	35
A-enolase	46
Arrestin	48
TULP1	78
PNR photoreceptor cell-specific nuclear receptor	41
Heat shock protein HSC 70	65

by reporting their initial cases [9]. Several years later, they reported the association of a 23-kDa band on Western blot from patients with CAR [11]. This band was subsequently identified to be caused by anti-recoverin reactivity [12]. Most of these patients also had other bands of anti-retinal antibody activity on Western blots, but as these were against unknown retinal proteins, they often went unreported initially. With time, some antigenic retinal proteins have been identified, but with the exception of anti-recoverin and α-enolase, no common pattern has emerged between the development of AIR (of all types), and specific grouping of anti-retinal antibodies [7]. What emerges as a pattern is that most patients who present with AIR signs and symptoms have multiple bands of anti-retinal protein activity on Western blots (untreated) [5, 8]. There are likely other immunologic factors, presently unidentified, that play further pathologic roles, as many retinal degenerations will also show activity on Western blots; comparative studies have not been done to define the key differences between patients who have active AIR disease and those where antibodies do not appear to be actively contributing to loss of visual function.

The association of AIR and the presence of carcinoma has been reported regularly, but in reality the association is uncommon [13]. The problem is to identify undiagnosed cases of carcinoma in freshly diagnosed cases of AIR. Carcinoma always needs to be ruled out with screening procedures including a careful medical history, a chest X-ray, and liver enzymes. A careful medical history may point to other areas that need testing to rule out a carcinoma. Typical types of carcinoma, which have been reported in CAR syndrome include lung, ovarian, and colon (Fig. 1). The large majority of AIR cases will not be found to have cancer. Several reports have shown that the tumors are making aberrant retinal proteins, which in turn stimulates an antigenic response as the proteins are no longer protected by the blood-retinal barrier created by the tight junctions of the retinal vasculature and the retinal pigment epithelium [1].

Most cases of CAR appear to be treatable as they seem to respond to lower levels of immunosuppression (Fig. 1; Table 2). This may be in part because most patients are also receiving chemotherapy, or the autoimmune pathologic processes in CAR may be less aggressive than typical npAIR. Prednisone, if tolerated, may often stabilize or even reverse visual field loss, but has to be given over a longer term. If the patient is shown to have anti-recoverin antibodies in the face of carcinoma, then the diagnosis of CAR is certain. How often CAR patients do not have anti-recoverin antibodies but show positive results on Western blots is not known. These patients typically have at least two or three clear bands on Western blot. Another unknown factor is whether the presence of the anti-retinal antibodies may be playing a role in controlling the tumor. This speculation has been raised in both CAR and MAR patients. Cases of melanoma regression in MAR patients have been reported in rare patients, so the question of whether treating the retinopathy could make the tumors worse has been raised [27]. Conversely, not treating the retinopathy may leave the patient blind, when it is generally preventable with treatment. So far, no clear cases of making tumors worse with immunosuppression have been cited.

Melanoma-associated retinopathy (MAR)

Initial cases of autoimmune retinopathy (Table 1) in association with skin melanoma were puzzling as these

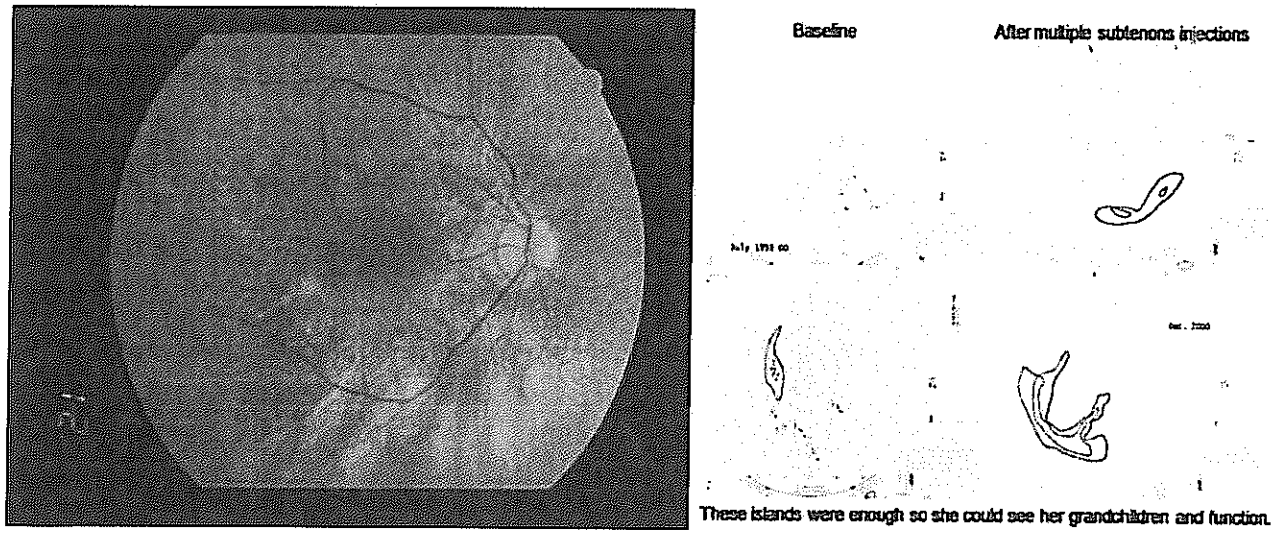

Fig. 1 A 79-year-old woman with ovarian carcinoma who developed CAR syndrome. Her internist would not allow systemic immunosuppression, so monthly subtenons injections were given, which maintained peripheral visual fields for the next 16 months of her life

cases clinically looked like CAR, but anti-recoverin antibodies were not found, and reportedly some MAR cases had no detectable antibodies by Western blot. Milam found that many of these cases showed positive bipolar staining on indirect immunofluorescence studies, using patient sera on normal human histologic slides, and then counterstaining for human immunoglobulin, which brought out the anti-bipolar antibody activity in the MAR patients [8, 23–26]. Initially, this specific staining was thought to be pathognomonic for MAR, but subsequently, our lab has had seven MAR patients, and only one had bipolar staining; but all cases otherwise met diagnostic standards and patterns for MAR (Fig. 2). All had activity on Western blots.

MAR patients have a more specific pattern than npAIR patients. They have similar symptoms at the onset, but then develop central and paracentral scotomata. Importantly, they generally have negative waveforms on standardized electroretinographic testing. Most have a generalized depigmentation of the retina, and vascular attenuation, like other forms of AIR [21–22]. The authors have evaluated MAR patients with skin, choroidal, and ciliary melanomas who have AIR and the above findings.

The most unusual case was an 86-year old gentleman who had a darkly pigmented nevus in his right eye that appears to have stimulated AIR process. There was severe diffuse atrophy around the nevus, and the eye was almost blind with peripheral islands, while the other eye had central visual field loss, and the patient had abnormal ERGs with negative waveforms.

The definitive test in the literature to establish MAR syndrome is to test the patient's serum (IgG) by indirect immunofluorescent histology to see if there is reactivity against normal donor retina bipolar cells. Some of these patients also have Western blot activity against soluble retinal proteins, and several have shown anti-recoverin activity. Many patients with positive Western blots will also light up specific cell types on indirect immunohistology in normal retina, but it is not yet known how well this correlates with pathogenicity. Cytotoxic studies have been done, which suggest toxicity by various antiretinal antibodies [13, 14].

Non-paraneoplastic autoimmune retinopathy

The majority of patients that present with the signs and symptoms of AIR do not have carcinoma or melanoma, and the etiology of their condition is often a mystery. The majority has a family history of at least several family members who have other autoimmune diseases, so presumably they have inherited a susceptibility to develop some autoimmune health conditions. Most of these patients will give a history of other conditions such as asthma, strange reactions to medications, or a known autoimmune condition such as hypothyroidism. Some atypical cases with asymmetric involvement give a history of head trauma preceding their onset of symptoms.

AIR is an inconsistent complication occurring in a number of retinal disorders including retinitis pigmentosa, where patients develop cystoid macular changes (Figs. 3 and 4), and a few may show a faster-than-usual visual field loss compared to typical RP [15, 16]. Patients with AZOOR, MEWDS, blindspot syndrome, birdshot retinopathy have all had autoimmune mechanisms suggested with

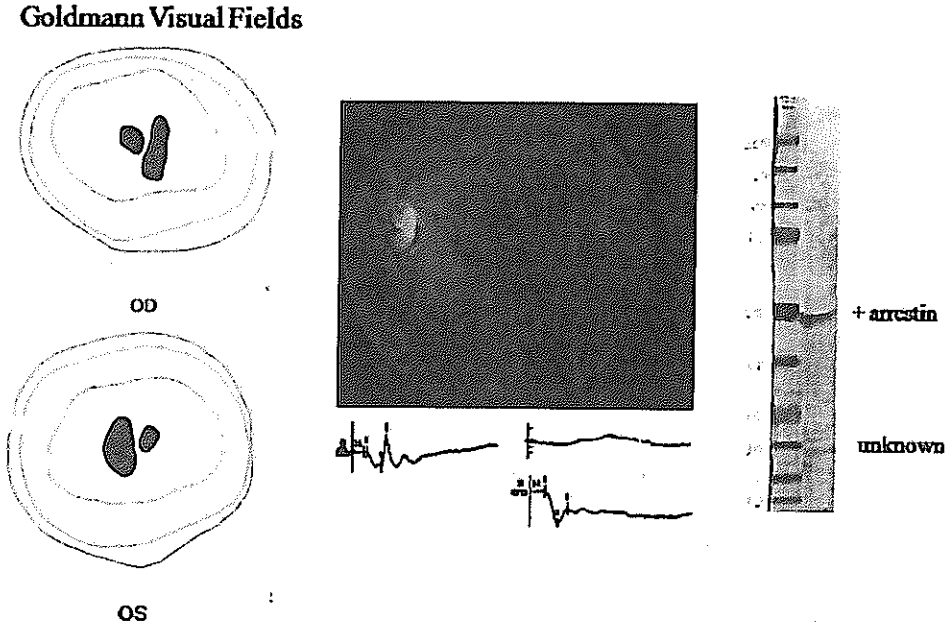

Fig. 2 A 75-year-old lady who had a toe removed for melanoma 1998 had a lymph note dissection. Interferon Rx, knee replacement 2003, visual symptoms started 2 months after knee surgery. Electroretinogram shows attenuation of photopic and scotopic waveforms and negative waveform in maximal stimulation mode

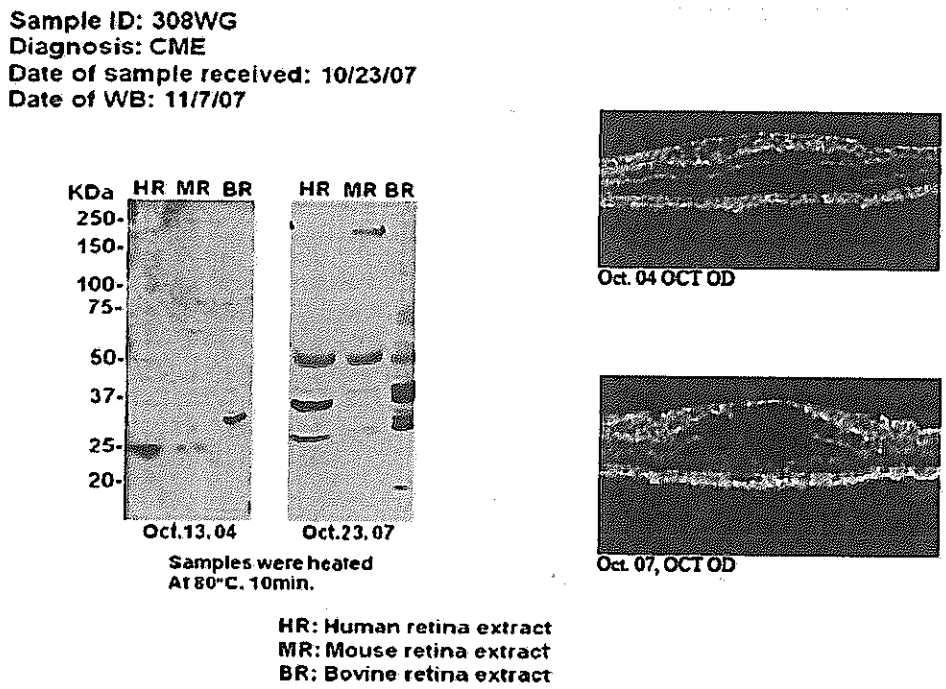

Fig. 3 Cystoid Macular Edema (CME) in pigmentary retinopathy (poor treatment). This 46-year-old lady was first evaluated for a pigmentary retinopathy in October, 2004. At that time, her vision was OD 20/30, OS 20/200. Her electroretinogram values were asymmetric, with the right eye having a photopic ERG that was 70% of normal and the left eye with all parameters about 50% of normal. By the following year, the ERG loss was symmetric between eyes about 40%. She had cystoid edema in both maculae, confirmed by OCT. Fundus examination showed pigmentary deposits in the peripheral retina. She also has a rheumatoid arthritis and a mixed vascular collagen disease. She was placed on immunosuppression in January 2005 for her cystoid edema, but she stopped her medications 5 months later because she could not tolerate the side effects. She returned in October 2007 with a visual acuity of OD 20/40 and OS 20/400 with increased antibodies on Western blot, and her CME was worse

variable evidence. However, the main feature that suggests an autoimmune component is that some of these patients develop negative waveforms on their ERG, and visual field loss or scotomata. The above are all common features that many AIR patients share [3] The diagnosis can be made by specifically measuring for anti-recoverin antibodies, or as proven to be pathologic other anti-retinal antibodies. Others antibodies that have been suggested are against α-enolase, transducin-β, HSP70, carbonic anhydrase II, and TULP-1 [13, 18, 1, 17]. The latter need more rigorous research investigations to better determine how much credence for causing AIR can be given if these antibodies are found. However, if a patient is showing multiple strong bands on Western blot, and has the signs and symptoms listed earlier, a tentative diagnosis of AIR can be made. The hallmark of AIR is a quick onset of symptoms and progression, and then an abnormal ERG. If the patient has a negative waveform under these conditions, the diagnosis is likely. However, until there is definitive diagnostic blood testing for AIR, weighing all evidence for the diagnosis will be necessary. An occasional RP patients without AIR may present with negative waveforms. Enzyme-linked immunosorbent assay (ELISA) testing and a Western blot will help to clarify their status.

Treatment of AIR

Once a diagnosis of AIR (including CAR and MAR) is made, a diagnostic treatment plan should be devised. AIR is a systemic disease, i.e., autoimmune antibodies are directed against the retina, and presently the best long-term treatments are immunosuppression. Short-term treatment can be done, such as intravitreal triamcinolone, subtenons depomedrol, or IV IgG infusions, but these do not treat the basis of the disease and longer term immunosuppression is still the best method (Fig. 4). Antioxidant vitamins such as beta-carotene (non-smokers), lutein, vitamin C, and vitamin E (non-cardiac patients) can be used also to help manage the retinal degeneration.

Many ophthalmologists work in collaboration with rheumatologists because of their familiarity in working with immunosuppressants. There will be some patients in whom the diagnosis is suspected, and a treatment trial to one eye with subtenons depomedrol (40–80 mg) may be tried to help prove the diagnosis before starting systemic immunosuppression. Normally, it takes two injections over an 8-week period, and testing with a kinetic visual field or ERG to measure for improvement against a baseline.

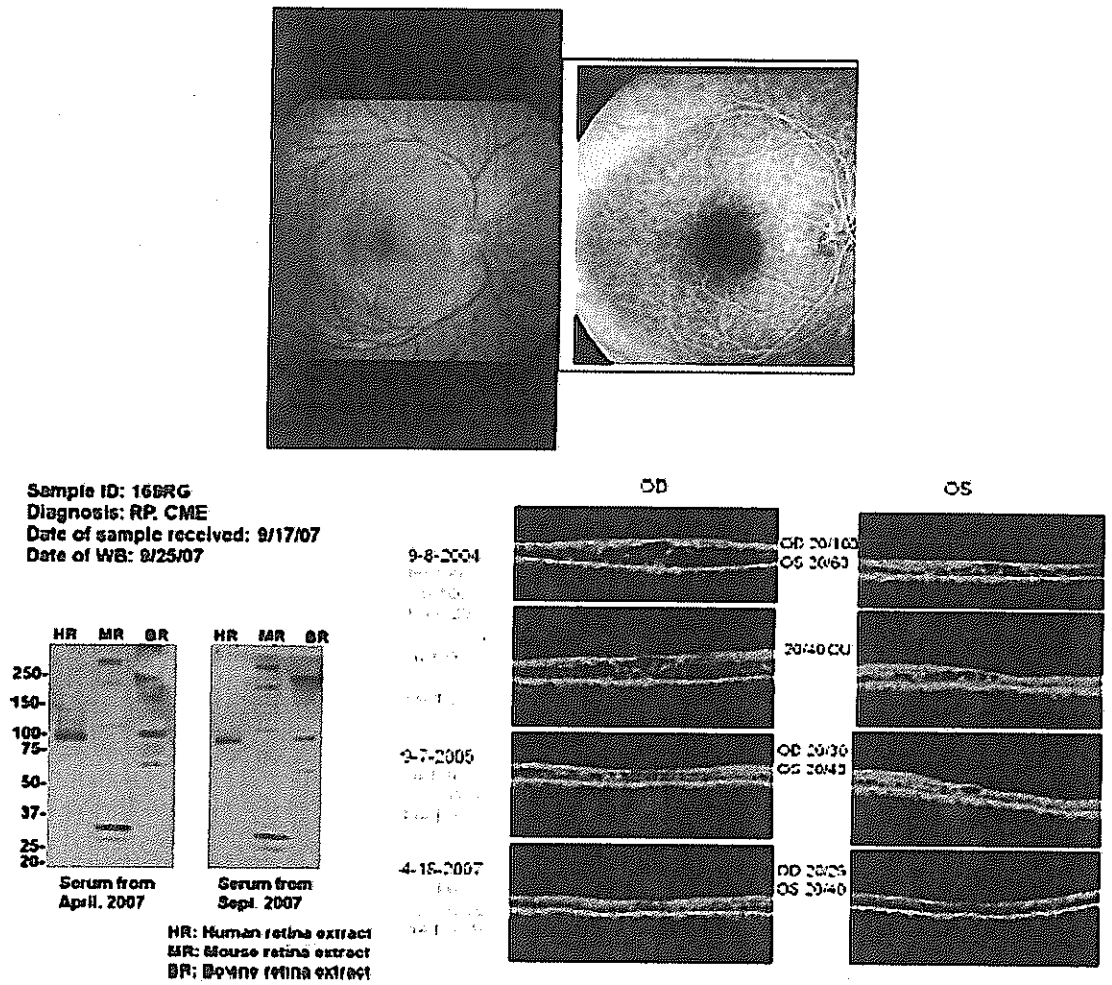

Fig. 4 Autoimmune retinopathy with treated CME. Right eye of 28-year-old man with panretinal degeneration and history of his grandmother having RP. He had a negative waveform on bright flash dark-adapted ERG, a flat rod-isolated, and 50% Photopic ERG with delayed implicit times. His cystic schisis-like changes of posterior pole did not show leakage on fluorescein angiography. circulating antibodies. Initial VA 20/200 in 2003 went to 20/25 on cyclosporine (CS), imuran (IM), prednisone (pred), while his cysts, and his Western blot showed minimal reactivity to human retina extract. The band at about 98 kDa is seen in normal controls also

Likewise with systemic immunosuppression, visual fields, and occasionally standardized ERG testing are effective for measuring treatment effects. Optical Coherence Tomography (OCT) is especially effective in measuring treatment effects in RP cystoid edema.

One important point about managing RP cystoid changes is that once treatment is instituted, systemic immunosuppression is needed to treat the cause of the antibodies. This is particularly true when *intravitreal triamcinolone* is used to reduce the cysts. Care should be taken to make sure that retreatment is given when the cysts start recurring. A pattern of reduction and expansion of the cysts causes significant damage to the macular with each cycle, and has to be avoided by early retreatment. Most patients who go through three cycles of re-expansion will not show any improvement on retreatment after the third cycle.

Table 2 Summary of AIR patients (all types) treated with various Immunosuppresants by the senior author

	Combined	CAR	npAIR	RP/CME
Total	31	6	16	9
Responders	19	5	8	6
Nonresponders	12	1	8	3
%	61	83	50	66
Age(median)	51	79	51	24
Gender M/F	8/23	2/4	4/12	2/7
AI Fam. Hx	77%	66%	87%	24%

Cases had a minimum of two follow up visits and consistently took medications.

CAR cancer associated retinopathy, *npAIR* non-neoplastic associated autoimmune retinopathy, and *AI* autoimmune

It is important to remember that there are seldom quick therapeutic fixes with AIR, and it takes chronic immunosuppression to stabilize and regain what retinal function is left (Figs. 3 and 4). We have found that CAR patients seemed to respond more quickly and to lower doses of immunosuppresants. Typically, patients on immunosuppression need at least 4 months to show improvements on visual field testing and treatment course may be needed for a year or more. Indicators for tapering treatment (or leaving patients on a maintenance doses) may be reaching an improved and steady level of function, with disappearance of bands on the Western blot. Patients with macula edema can be followed clinically, with visual acuities, fluorescein angiography, and OCT testing. Some patients have macular cysts from a schisis-like process, and the OCT is best for following their progress.

A few cases who met normal diagnostic criteria for AIR spontaneously stopped their immunosuppressive medicines, but maintained large doses of antioxidant vitamins, and seemed to show some stabilization of their visual fields. This phenomenon needs study, but as AIR patients are rare, and many do need immunosuppression, it will take a careful study design to clarify the best methods of treatment.

Autoimmune retinopathy is a complex disorder, and often does not present in a fixed pattern, presumably because different combinations of anti-retinal antibodies are present from patient to patient, and the various combinations of antibodies result in variations in disease expression. Other factors such as blood–retinal barrier integrity, and family history of autoimmune diseases can influence the severity. We found that patients with autoimmune family histories seemed to be more difficult to treat than other AIR patients (Table 2). Because circulating anti-retinal antibodies are present in patients with many retinal diseases, the challenge is to determine which ones are pathogenic and or benign, and what other factors are present that cause anti-retinal antibodies to become pathologic. Definitive tests are needed to more quickly diagnose AIR/CAR/MAR patients so that therapies can be started earlier in the disease process.

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