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## AUTOIMMUNE RETINOPATHY-A REVIEW

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### ABSTRACT

Autoimmune retinopathy is a rare autoimmune disease that primarily affects retinal photoreceptor function. It mainly presents in the fifth and sixth decades. Three main forms of autoimmune retinopathy (AIR) have been identified: 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. Patients typically present with a sudden onset of photopsia, rapid visual loss, and abnormal electroretinograms (ERGs). Different types of AIR present with similar clinical features and it requires extensive work up to rule out other differential diagnosis. Pt presents with poor visual prognosis that may be due to delayed diagnosis and delay in initiation of treatment. Different treatment modalities have been tried, including systemic immunosuppression with steroid and steroid-sparing agents, intravenous immunoglobulin, and plasmapheresis, with variable results. Different types of antiretinal antibodies have been found in these patients with autoimmune retinopathy such as antibodies to recoverin,  $\alpha$ -enolase and transducin- $\alpha$ , but seronegative disease is also common. A lot of research work has been done in this field to understand the pathophysiological mechanisms that is responsible for autoimmune retinopathy, but than also understanding about this rare disorder is limited. In this review we have tried to summarize the pathogenic mechanism, clinical features, investigation, differential diagnosis, treatment and prognosis of autoimmune retinopathy.

**Keywords**-Autoimmunity, Retinopathy, Autoantibody

### INTRODUCTION

Auto immunity is a condition in which ones own tissues are prone to be affected by deleterious effects of the immunological system. Autoimmune retinopathy occurs when antigens trigger an immune response, which produces antibodies those cross reacts with a retinal protein. Autoimmune retinopathy represent an important cause of an otherwise unexplained acute or sub-acute vision loss in adults. These forms of retinal disease result from a presumed immunological process affecting the retina by auto antibodies directed against retinal antigens<sup>(1-3)</sup>.

Autoimmune retinopathies can occur:

1. Rarely as primary autoimmune retinopathy.
2. More commonly as.
  - a. Cancer associated retinopathy (CAR)
  - b. Retinopathies secondary to various autoimmune reactions.

Cancer associated retinopathy is the term that has been used for the retinal degeneration first described by Sawyer & associates<sup>[4]</sup> in 1976 as a distant effect of cancer. Paraneoplastic retinopathy, a term first used by Klingele & associates in 1984<sup>(5)</sup> has become the more general term used for any of a number of autoimmune

retinopathy associated with a malignant tumor. Autoimmune retinopathy is the preferred term for an acquired, presumed immunologically mediated retinal degeneration with symptoms resembling paraneoplastic retinopathy<sup>(2)</sup>.

The etiology & source of antigenic stimulation vary but are largely unknown. It is possible that the disease is triggered by molecular mimicry between retinal proteins & presumed viral or bacterial proteins or by the acquired alteration of host tissues or antigen so that the autoimmunity is induced against retinal proteins. Multiple retinal proteins have been found to be antigen including recoverin, enolase, arrestin, transducin TUPL I, neurofilament protein, heat shock protein, 70 PNR and as yet unidentified bipolar cell antigen causing melanoma associated retinopathy (MAR syndrome)<sup>(6)</sup>.

Autoimmune retinopathies are ophthalmic disorders in which autoantibody damage retina and its components causing progressive vision loss. Autoimmune retinopathy typically presents in the fifth & sixth decades with rapidly progressive, bilateral, painless visual deterioration<sup>(7)</sup>.

Specific forms of autoimmune retinopathies that have been identified include cancer associated retinopathy (CAR)<sup>(4,8)</sup>, melanoma associated retinopathy (MAR)<sup>(6)</sup>, anti-enolase retinopathy<sup>(2)</sup>, anti-carbonic anhydrase retinopathy and cancer associated cone dysfunction<sup>(9)</sup>.

Some patients of secondary autoimmune retinopathy had associated systemic autoimmune diseases such as rheumatoid arthritis, grave's disease, systemic lupus erythematosus and antiphospholipid antibody syndrome<sup>(10)</sup>.

## EPIDEMIOLOGY

Autoimmune retinopathy is an uncommon disorder, exact prevalence not known. It usually affects older adults, but patients as young as three years have been described with no sex predilection<sup>(11,12)</sup>. Cancer associated retinopathy is most common form of autoimmune retinopathy. The malignancy most commonly associated with

disorders is small-cell lung cancer, followed by gynecological breast cancers. Some cases have been reported with Hodgkin's lymphoma, pancreatic and colon cancers<sup>(11,13)</sup>. MAR appears to be increasing in frequency relative to CAR, perhaps because of a decrease in cases of lung cancer<sup>(11)</sup>.

## CLINICAL FEATURES

Autoimmune retinopathy typically presents in the fifth & sixth decades with rapidly progressive, bilateral, painless visual deterioration but an unremarkable fundus examination<sup>(7)</sup>. Patients typically present with sudden onset of photopsia, rapid visual loss, and abnormal electroretinograms (ERG)<sup>(14)</sup>. Bilateral vision loss as a result of both rod & cone dysfunction in CAR may occur over a period of months, visual symptoms may precede diagnosis of the systemic malignancy<sup>(15)</sup>.

The triad of photosensitivity, ring scotoma, & a reduced caliber of the retinal arteriole along with undetectable signals in ERG are specific manifestations of CAR<sup>(16)</sup>. MAR is characterized by shimmering, flickering or pulsating photopsias & usually occurs in the patients with cutaneous melanoma<sup>(16)</sup>.

Besides glare sensitivity & flashing lights, a rapidly progressive, often asymmetric visual loss may occur. Although paracentral & mid-peripheral scotomas can be found frequently, visual field defects are often quite heterogeneous<sup>(17)</sup>.

### Individuals with cone involvement have

- Photosensitivity (light sensitivity)
- Prolonged glare after light exposure (hamarolopia)
- Reduced visual acuity and loss of vision.

### Patients with rod involvement have

- Difficulty in seeing in dim lighting (Nyctalopia).
- Prolonged dark adaptation.
- Peripheral field vision loss.

### Signs

- Decreased central visual acuity

- Visual field defects (central, paracentral or equatorial scotomas)
- Alternate pupillary defect if asymmetric involvement.
- Defective color vision.

### Fundus Findings

Fundus can appear normal initially but with progression there is evidence of retinal degenerations (Retinal pigment epithelium RPE thickening and mottling, attenuation of the arterioles, optic nerve pallor. Cystoid macular edema (CME) has been reported in patients with non paraneoplastic retinopathy (npAIR) but is less common with CAR<sup>(18,19)</sup>.

As reported by Keltner et al, fundus findings in 43 patients with MAR were as follows: 19 (44%) patients had normal fundus findings at presentation, 13 (30%) had vascular attenuation, and 12 (28%) had RPE changes. Vitreous cells were present in 13 (30%) patients, and 10 (23%) had optic disc pallor<sup>(11, 20)</sup>

### Investigations & Diagnosis

All the patients who presented with unexplained loss of central vision, visual field defects, and/or photopsia are diagnosed with AIR based on clinical features, ERG findings, serum antiretinal antibody analysis and OCT testing for macula<sup>(10)</sup>.

On OCT, patients show outer retinal abnormalities and/or decreased macular thickness. In Macular OCT reduced central macular, foveal thickness, loss of the photoreceptor layer or disruption of the photoreceptor outer & inner segment junction was noted<sup>(10)</sup>

Figure3

It should also be noted that antiretinal antibodies may be present in the normal population & their presence does not necessarily indicates retinopathy<sup>(10)</sup>. For example, while anti recoverin autoantibody is not typically present in the normal population, the frequency of anti- $\alpha$ -enolase autoantibody is approximately 10% in healthy

subjects; however this is not well defined for other anti-retinal auto antibodies<sup>(21,22)</sup>.

It was found that autoantibodies against retinal proteins from patients with retinopathy were cytotoxic to retinal cells, in contrast to those from healthy subjects, probably through recognition of additional unique regions on their target retinal antigen<sup>(23)</sup>.

Antibody Testing and their cytotoxic effects can be assessed with western blot, ELISA, immunocytochemistry, cytotoxicity assay for acute recovering antienolase antibodies assay<sup>(24)</sup>.

The literature varies in diagnostic criteria for AIR & firm establishment of this diagnosis is challenging.

There have been different antibodies isolated against many specific retinal proteins in patient with autoimmune retinopathies. Patients with CAR possess autoantibodies, including recovering (23KDa),  $\alpha$ -enolase(46KDa)<sup>(21,25)</sup>. Other autoantibodies against retinal proteins have also been reported such as neurofilament proteins, heat-shock protein 70, TULPI protein, 40KDa insoluble protein<sup>(21,25-30)</sup>. Auto antibodies binding to bipolar cells have been linked to the melanoma-associated retinopathy (MAR) syndrome<sup>(31-33)</sup>

### Table 1 ELECTRORETINOGRAM

- Typically, the responses in the ERG are markedly reduced, but normal ERGS are also described<sup>(17)</sup>. Full field ERG are almost always abnormal, attenuated or absent photopic and scotopic response. IN CAR where mainly the cones are affected, full filed ERG could be normal but multifocal ERG will be abnormal.

### DIFFERENTIAL DIAGNOSIS OF AUTOIMMUNE RETINOPATHY

- Retrobulbar optic neuropathy.
- Toxic nutritional optic neuropathy or hereditary optic neuropathy.
- In malignancy unexplained visual loss may be due to infiltration of malignant cell around

optic nerves metastasis to orbit & optic neuropathy due to chemotherapeutic agents

- Acute Zonal occult outer retinopathy (AZOOR).

### TREATMENT

Treatment of primary disease should be done in conjunction with a physician and an oncologist. Long term immune suppression is the main therapy. Immunosuppression has been used to treat AIR with mixed results. Sawyer et al treated 1 of the original 3 patients with CAR with prednisone but saw no improvement<sup>34</sup>. Keltner et al reported the first patient with CAR responsive to corticosteroid therapy<sup>35</sup>. Since then, there have been numerous case reports in the literature using short-course high-dose intravenous methylprednisolone or oral prednisone. Plasmapheresis, when used alone, led to no improvement<sup>36</sup>, when used with prednisone, vision improved in 1 patient<sup>37</sup>. Guy and Aptsiauri reported improvement in 2 of 3 patients treated with intravenous immunoglobulin and stabilization in the third<sup>38</sup>. Espandar et al recently reported stabilization of CAR with alemtuzumab therapy<sup>39</sup>.

Various treatment modalities have been tried in patients with CAR, including oral and intravenous steroids, plasmapheresis, IVIg, rituximab, azathioprine, cyclosporine, and mycophenolate mofetil<sup>[40-43]</sup>. Despite treatment with these systemic medications, it is not unusual to have a progressive decline in vision with this disease<sup>44</sup>. Serial intravitreal injection of triamcinolone may be beneficial for maintenance of vision in patients with CAR<sup>44</sup>.

### PROGNOSIS

Treatment may provide mild to moderate transient visual acuity improvement. But overall the visual prognosis remains poor. In cases of CAR, systemic cancer treatment usually do not lead to visual improvement However prognosis depends on their underlying malignancy<sup>(16)</sup>.

### DISCUSSION

The diagnosis of autoimmune retinopathy remains extremely challenging. Patient has to undergo extensive neurological & neuro- ophthalmological evaluation it also should be noted that antiretinal antibodies may be present in the normal population & their presence does not necessarily indicate retinopathy.

Different mechanism of cell damage have been suggested for anti recoverin<sup>(45,46)</sup> and anti-enolase antibodies<sup>(47,48)</sup> predominantly resulting in apoptosis of retinal cells, therefore it appears that apoptosis may be a common pathway for retinal autoantibody induced retinal degeneration.

The evidence supporting the effects of antibodies on retinal cells are the following findings:

a) Autoantibodies against recoverin specifically labeled retinal photoreceptor cells and were internalized by cells causing their apoptotic death<sup>[49]</sup>.

b) In CAR patients, autoantibodies against  $\alpha$ -enolase induced the apoptotic death of retinal cells, and in glaucoma patients, autoantibodies against  $\gamma$ -enolase labeled retinal ganglion cells and induced their death through apoptosis<sup>[50,51]</sup>

Independent of specificity, autoantibody-induced apoptosis is a pathway to retinal death in AR.

However the pathogenic mechanisms of retinopathies are complex and our understanding of AR is still incomplete. Further studies are necessary to identify anti-retinal autoantibodies, to test their pathogenic potentials through *in vivo* and *in vitro* methods, and to define clinical and electrophysiological indicators for seropositive patients.

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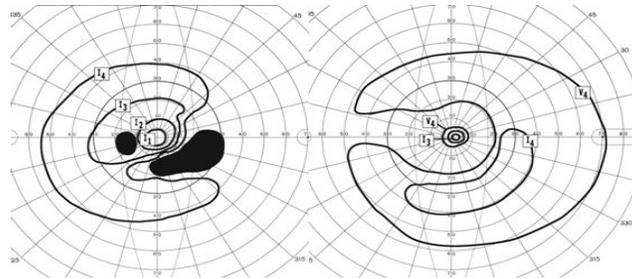
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**Table 1 Autoantibody specificity in patients with retinopathy of systemic cancer**

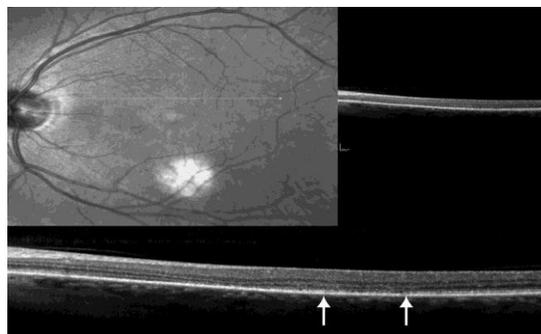
S. No.	Cancer	Antibody Specificity
1.	Endometrial Ca	Recoverin
2.	Skin Melanoma	Enolase
3.	SCCL	Recoverin
4.	Cervical Ca	Enolase
5.	Ovarian Ca	P35, P39, P46, P58
6.	Breast Ca	Enolase



**Figure 1.-Goldmann perimetry in a patient with bilateral sequential visual loss and photopsias. In the right eye, there is a dense ring scotoma breaking out to the periphery. In the left eye, there is an inferior arcuate scotoma that breaks out nasally<sup>(11)</sup>.**



**Figure 2-Fundus picture of a patient with AIR<sup>(52)</sup>**



**Figure3- Spectralis SD-OCT of left eye. Area of “moth-eaten” photoreceptor inner segment/outer segment abnormalities can be seen between the arrows in an area that appeared normal on funduscopic examination<sup>(53)</sup>.**