Autoimmune Retinopathy

Patients With Antirecoverin Immunoreactivity and Panretinal Degeneration

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Purpose: To investigate whether antirecoverin antibodies are present in patients with retinitis pigmentosa (RP). Recoverin, a retinal protein, has been implicated as a cause of cancer-associated retinopathy (CAR), which manifests as an RP-like retinal degeneration. The rationale is that the ocular findings in CAR syndrome are similar to those found in many forms of RP, and since 40% of patients with RP have no family history, some patients may have an underlying autoimmune process causing or contributing to their retinopathy.

Methods: Serum samples from 521 patients diagnosed with RP were screened for antiretinal proteins activity by Western blot analysis. Fifty-one patients had antibody reactivity against retinal proteins in the range of 23 to 26 kd and underwent dot-blot analysis for antirecoverin antibody, checking IgG and IgM antibodies. Enzyme-linked immunosorbent assay (ELISA) was performed to evaluate the titer of antirecoverin antibodies in patients with positive results on dot-blot analysis. Lymphocyte proliferation assays using recoverin were performed on 26 samples.

Results: Ten patients were found to have antirecoverin antibody and/or cellular immunoreactivity. Eight patients had positive dot-blot testing: 6 patients had both IgG and IgM antirecoverin activity, and 1 patient each had IgG or IgM activity. In these 8 patients, numerous other antiretinal protein antibodies were present. Three patients had positive recoverin-mediated lymphocyte proliferation, and all patients were positive for antirecoverin antibodies on ELISA testing.

Conclusions: Antirecoverin immunoreactivity was found in 10 patients without systemic malignancy but with clinical findings consistent with RP. These results suggest that there are other immunogenic mechanisms occurring in the formation of antirecoverin antibodies in addition to the putative tumor-mediated mechanisms. This survey suggests that there may be rare cases of CAR-like syndrome in the category of simplex RP, or that some patients with RP also have antirecoverin antibodies that may be exacerbating their underlying disease.


The concept of autoimmune retinopathy has been established by various publications on cancer-associated retinopathy (CAR syndrome).1-7 Initially, it was noted that rare cancer patients developed a bilateral idiopathic panretinal degeneration.8 Kellner et al9 were the first to pose the autoimmune theory of cancer-induced blindness. Investigations by Thirkill et al3 identified a 23-kd protein on Western blot against which antibodies were formed in patients with CAR. Subsequently, the antigenic protein was identified to be recoverin, an important photoreceptor component involved in turning off the visual cascade.10-12 The pathogenic autoimmune mechanisms involved in CAR syndrome are not well understood, but there is evidence that patients are sensitized by recoverin expressed by their tumors, which in turn creates an immune response against retinal-expressed recoverin.13 This theory has been validated in reports in which 3 patients with CAR syndrome and positive antirecoverin antibodies have demonstrated recoverin protein in their malignant tumors.14,15

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In addition to antirecoverin antibody, patients with CAR consistently demonstrate other antiretinal antibodies on Western blot. In the original report in which antirecoverin antibody was identified as the cause of CAR syndrome, Western blot results from these patients demonstrated a number of unidentified...
PATIENTS AND METHODS

All patients underwent clinical evaluation for retinal degeneration by one of us (J.R.H.) at the Jules Stein Eye Institute, Los Angeles, Calif. The basis for inclusion in the study was the presence of bilateral pigmentary retinopathy, irrespective of hereditary pattern. Many cases normally would fall in the category of typical RP, but some cases were atypical, with diffuse atrophy and no pigment deposits, or with severe retinal striae. All patients had severely abnormal ERG findings, moderate to severe visual field loss, night blindness, diffuse retinal atrophy, and vascular attenuation. A family history for retinal disease was obtained from each patient. The clinical evaluation for each patient consisted of an ERG, kinetic visual field, ophthalmoscopy, and fundus photography.

At the time we compiled our data for analysis, 521 patients with retinal degeneration had given informed consent and blood samples for the study. On reviewing medical histories, no patient was found to have cancer at the time of blood draw, and those with antirecoverin antibodies were requested to undergo evaluation to rule out carcinoma. Blood samples were drawn by means of venipuncture from the antecubital space or back of hand, allowed to clot, and centrifuged. The serum samples were sent immediately by Federal Express to the University of Florida, Gainesville, for evaluation using Western blot analysis for presence of antiretinal antibodies. Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) was performed under reducing conditions according to Laemmli.14 Human retinal protein extract or recombinant or purified retinal proteins were separated on 12% SDS-PAGE slab gels, and transferred to polyvinylidene fluoride (PVDF) membrane. The patients' serum samples were diluted 1:200 and placed on the PVDF membrane for 2 hours. The blots were washed 3 times with phosphate buffer solution (PBS) and subsequently incubated with secondary antibody (alkaline phosphatase–conjugated goat anti–human IgG or IgM (Sigma-Aldrich, St Louis, Mo; diluted 1:4000). The color reaction was developed using a substrate for alkaline phosphatase (BCIP/NBT; Zymed, San Francisco, Calif).

Antinuclear antibody (ANA) testing was performed on all serum samples that were positive on dot-blot analysis for antirecoverin activity. Hep-2 substrate slides (Sanofi Diagnostics Pasteur, Inc, Chaska, Minn) were incubated with patient serum sample, rinsed in PBS, then incubated with appropriate conjugated goat anti–human IgG and IgM were used as the secondary antibodies. Color reaction was developed by addition of peroxidase substrate in buffer containing 0.03% hydrogen peroxide and measured at 405 nm.

Lymphocyte proliferation assays (LPAs) were performed on mononuclear cells from 26 patients and healthy volunteers. Mononuclear cells were separated from peripheral blood samples using Ficoll-Histopaque density gradient centrifugation, and cultured with or without recombinant recoverin (15 μg/mL). Proliferative responses of cultured cells were assayed by measuring incorporation of 1 μCi of [3H]-thymidine. Results were presented as stimulation indices calculated as mean counts per minute of cultures with stimulant divided by mean counts per minute of the unstimulated control culture. Stimulation was considered positive if the stimulation index was at least 2.0.

The ELISA assay was performed on microtiter plates coated with recombinant recoverin, 0.4 μg per well. The serum samples were added at 2-fold serial dilutions (100 μL per well) starting with a dilution of 1:20. Peroxidase-conjugated goat anti–human IgG and IgM were used as the secondary antibodies. Color reaction was developed by addition of peroxidase substrate in buffer containing 0.03% hydrogen peroxide and measured at 405 nm.

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Patients who had immunoreactive bands in the 23- to 26-kd region, corresponding to recoverin, underwent further screening using dot-blot analysis and enzyme-linked immunosorbent assay (ELISA) to check for specificity. For dot-blot testing, recombinant recoverin (courtesy of James Hurley, PhD) was used in the amount of 0.5 μg per dot. The ELISA assay was performed on microtiter plates coated with recombinant recoverin, 0.4 μg per well. The serum samples were added at 2-fold serial dilutions (100 μL per well) starting with a dilution of 1:20. Peroxidase-conjugated goat anti–human IgG and IgM were used as the secondary antibodies. Color reaction was developed by addition of peroxidase substrate in buffer containing 0.03% hydrogen peroxide and measured at 405 nm.

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antibodies to be present.12 Retinal proteins that have been identified to have antibodies against them include the protein enolase,17 whereas other reports suggest that antibodies to heat shock cognate protein-70 are found in some patients with CAR.18 Other proteins that frequently are targeted by antiretinal antibodies on Western blot are found at 60 kd, 62 kd, 70 kd,19 and 43 kd,20,21 but the identity of these retinal proteins is not yet known.

Clinically, patients with CAR syndrome relate a sudden onset of night blindness, which may start before or after their tumors are identified. The visual field and central vision loss is moderately rapid and occurs over a period of months to a few years. Early on, the fundus changes can be subtle, consisting of mild retinal vessel attenuation and diffuse panretinal pigment epithelial depigmentation that gives a blond appearance to the fundus. Initially, although the patient often complains of photopsias and night blindness, the diagnosis of panretinal degeneration may be missed. However, if the suspicion is raised, an electoretinogram (ERG) will consistently be abnormal, which establishes the diagnosis of retinal degeneration. By the time patients undergo an evaluation for CAR syndrome, the ERG often is extinguished.

We initialized screening for antirecoverin antibodies in patients with retinitis pigmentosa (RP) because we were confronted with a handful of patients who manifested signs and symptoms of CAR syndrome, but whose extensive medical evaluations were negative for carcinoma. Usually these patients had the diagnosis of simplex RP. We wanted to investigate whether these patients with CAR-like syndrome had circulating antirecoverin antibodies, and whether antirecoverin and other antibodies are present in patients with RP. Therefore, all patients seen with RP from January 1, 1995, through December 31, 1998, underwent screening for antirecoverin antibodies.
RESULTS

Of the 521 serum samples analyzed by Western blot, 51 had immunoreactive bands in the 23- to 26-kd region. In Western blots, 1-dimensional gel electrophoresis proteins are separated by size (or molecular weight) only, usually denoted as kilodalton bands. Because the size of the protein is not enough to identify it (there are many different proteins of the same approximate weight), additional tests are necessary to confirm the identity of the protein. We used dot-blot testing to specifically identify reactivity against recoverin, and further analyzed the specific class and levels of immunoglobulins by ELISA technique.

Positive immunoreactivity against recoverin was documented in 10 patients (Table 1). Six patients had IgG and IgM serum antirecoverin antibodies, whereas 1 patient had IgM and another patient had IgG antirecoverin antibodies. All patients were positive for antirecoverin antibodies on ELISA testing. Of the 26 patients who underwent the LPA testing, 2 patients had isolated LPA activity without positive reactivity on dot-blot testing for antirecoverin immunoglobulins, whereas 1 patient with positive findings for IgG and IgM antirecoverin antibodies also had an abnormal stimulation index on LPA testing with recoverin (Table 1).

The serum samples of all patients with antirecoverin immunoreactivity demonstrated several positively labeled bands (other than 23 kd) on the 1-dimensional Western blots. Since the retinal proteins on most of these bands are not currently identifiable, it is not possible to speculate on whether they have a pathophysiological role.

The presence of multiple bands of immunoglobulins suggested the possibility of an underlying systemic autoimmune condition in these patients. To investigate this possibility, we performed ANA testing of the serum samples, and found no difference in ANA-positive results between patients and the control group of healthy donors.

The clinical characteristics of the patients with positive results of antirecoverin testing are presented in Table 2 and Figures 1, 2, 3, 4, 5, and 6. Patients included 5 women and 5 men, with ages of onset ranging from 20 to 60 years and a mean of 36.9 years. Initial visual acuity for these patients ranged from 20/20 to counting fingers in the better eye. Duration of follow-up ranged from 3 to 18 years. Goldmann visual fields at initial examination ranged from 2° central islands to 45° with equatorial scotomata, measured with the IV-4e target. All but 1 patient (case 3) had evidence of cystoid macular edema at some time during follow-up (Figure 1, Figure 2, and Figure 3), and 8 of 10 patients had cystoid macular edema at initial examination. Bone spicule–like pigment was found in 3 of 10 patients, whereas the others had minimal pigmented retinopathy (Figures 1-6 per quadrant) or no pigment. The ERGs were nonrecordable or barely recordable in all but 2 patients (cases 4 [Figure 2] and 9), who were seen initially with a rod-cone pattern of ERG change. Family history was positive for consanguinity in 1 patient (case 4), and 2 patients (cases 3 and 7) had siblings with documented panretinal degeneration, suggesting multiplex inheritance. Most patients (7/10) had no family history of panretinal degeneration.

COMMENT

Autoimmune retinopathy is emerging as an important diagnosis in a subgroup of patients with signs and symptoms of RP, but their recent onset of unexplained visual loss often progresses at a more rapid rate than typical RP. These patients have associated electrophysiologic and visual field evidence of retinal degeneration, but medical evaluation fails to reveal any evidence of malignancy. Many patients with autoimmune retinopathy (CAR-like syndrome) differ from those with typical RP in that they seldom have pigmentary deposits and, in our experience, frequently have posterior pole retinal wrinkling, characterized by retinal thickening in the posterior pole and radiating retinal folds as illustrated by case 1 (Figure 1). The diffuse retinal atrophy in the peripheral fundus tends to give a very blond appearance, as illustrated by cases 1, 2, 3, 5, and 7 (Figures 1,
2, 4, 5, and 6). The reality is that patients with autoimmune retinopathy can be very difficult to distinguish from patients with RP, particularly those with RP sine pigmento.

The presence of serum autoantibodies that bind with retinal proteins on Western blot analysis suggests autoimmune activation in these patients with CAR-like syndrome against a variety of retinal antigens, of which only a few have been isolated and identified. Although Western blots detect IgG and IgM antiretinal protein antibodies, the test does not tell whether the antibodies are pathologic, which will require other methods of investigation. Recently, Ohguro et al18,25 published a report demonstrating that antirecoverin and heat shock cognate protein 70 were found together in 4 of their patients with CAR, and in testing the antibodies in Lewis rats, they found that the pathologic effects of antirecoverin antibodies were greatly enhanced in the presence of

| Table 2. Clinical Characteristics of Patients With Antirecoverin Antibody Activity* |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Patient No./Sex/ Age at Onset, y Rate of Visual Loss by History Inheritance Initial VA | Follow-up, y | Initial GVF | Pigment Deposit Anterior Retina | Initial ERG, % From Mean for Age† | Final VA | History of Tumors |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 1/F/22 Fast, lost visual function over 2 y | S | OD 20/60; OS 20/60 | 7 | Equatorial scotomata, both eyes; residual island 40° | Posterior pole edema | None | Nonrecordable | OD 10/160; OS 10/100 | Ovarian cyst |
| 2/M/60 Sudden loss right eye; over 2 y left eye | S | OD 20/60; OS 20/40 | 6 | Central island 10° | Mild | None | Photopic, barely recordable; scotopic, nonrecordable, both eyes | OD 20/80; OS 20/100 | None |
| 3/F/50 Slow, typical RP course | Mx | OD CF; OS CF | 18 | Paracentral island 2° | Negative | Posterior pole; minimal | Photopic B wave, delayed implicit time; rod-isolated B wave, 40%; max scotopic A wave 20%; max scotopic B wave, 30% | OD LP; OS HM | None |
| 4/F/40 5-year history similar to RP | Possible AR (consanguinity) | OD 20/200; OS 20/40 | 6 | Equatorial scotoma 35° both eyes; central scotoma 5° right eye | Severe edema; posterior pole; both eyes | Nonrecordable | OD CF; OS 20/50 | Ovarian cyst |
| 5/M/40 Fast (4-5 mo) | S | OD 20/40; OS 20/30 | 6 | Central islands 5°; temporal islands 25° | Mild | None | Nonrecordable | OD 20/200; OS 20/80 | Basal cell tumor, removed |
| 6/M/22 Slow (years) | S | OD 20/20; OS 20/20 | 3 | Equatorial scotoma; remaining island 45° | Mild | Minimal | Nonrecordable | OD 20/20; OS 20/20 | None |
| 7/F/40 Initial fast changes during 1 y | Mx | OD 20/40; OS 20/30 | 9 | Equatorial scotoma; remaining islands 55° | Mild | Minimal | Barely recordable | OD 20/200; OS 20/200 | None |
| 8/F/20 Slow (years) | S | OD 20/25; OS 20/40 | 18 | Equatorial scotoma; remaining island 20° | Posterior pole edema, macular hole, right eye | Moderate | Photopic barely recordable; scotopic nonrecordable | OD CF; OS 20/50 | None |
| 9/M/30 Slow (years) | S | OD 20/40; OS 20/40 | 10 | Equatorial scotoma; remaining island 35° | Moderate | Moderate | Photopic B wave 88%; Rod-isolated B wave 33%; Max scotopic A wave 64%; Max scotopic B wave 46% | OD 20/200; OS 20/300 | None |
| 10/M/45 Changes over 2 y | S | OD 20/30; OS 20/25 | 12 | Equatorial scotoma; remaining island 30° | Mild right eye | Minimal | Nonrecordable | OD 20/40; OS 20/40 | None |

*VA indicates visual acuity; GVF, Goldmann visual field; CME, cystoid macular edema; ERG, electroretinogram; VA, visual activity; S, simplex; RP, retinitis pigmentosa; Mx, multiplex; LP, light perception; HM, hand motions; AR, autosomal recessive; Max, dark-adapted bright-flash ERG; and CF, counting fingers.
†Scotopic ERG indicates rod isolated.
heat shock cognate protein 70. This association will need to be studied in future investigations to determine its significance in patients with autoimmune retinal degeneration without cancer.

In the past, antirecoverin antibodies were considered to be a specific marker of CAR.26 Our findings as well as those of Whitcup et al27 have revealed another group of patients with retinal degeneration who have antirecoverin autoimmunity without cancer. These patients can present a diagnostic dilemma for the clinician, since they are difficult to distinguish from patients with CAR, clinically and using laboratory studies. Five of our patients (Table 2, cases 1, 2, 5, 7, and 10) gave histories of rapid changes in their vision associated with photopsias over a short period of weeks to several months, a finding that is similar to histories given by patients with CAR. In reviewing the ELISA antirecoverin titers of our patients, we found there was a wide range of activity that did not appear to correlate with severity of disease. In our minds, the patients with antirecoverin autoimmunity are often difficult to distinguish from those with CAR, and careful evaluation for the presence of cancer is recommended in cases of antirecoverin autoimmunity.

Recoverin, a 23-kd retina-specific intracellular photoreceptor protein, is a component of the visual transduction cycle. Recoverin was the antigenic protein originally associated with antibody response in CAR.10-12 The finding of recoverin expression in several small cell lung cancer tumors established a basis for the hypothesis that the eliciting mechanism for CAR syndrome is exposure of the immune system to recoverin antigen from the carcinomas.14-16 The cross-reactivity between tumor-expressed recoverin and photoreceptor recoverin is postulated as the responsible mechanism.28 Antirecoverin antibodies also have been associated with other lung carcinomas.29

The mechanism underlying the presence of circulating antirecoverin antibodies in our patients is not known. None of the 10 patients whom we are describing had carcinomas, but 3 had histories of benign tumors: cases 1 and 4 had ovarian cysts, and case 5 had a basal cell tumor. The relevance of this finding cannot be determined from our series, particularly as benign tumors are a common occurrence. Whitcup et al27 also reported the history of removal of a benign parotid tumor, associated with cellular immune reactivity to recoverin, in their patient.

The understanding of autoimmune retinopathy has expanded since the original reports of CAR. The absence of antirecoverin antibodies in patients with cancer and retinal degeneration simulating the CAR profile has prompted the search for other antibodies.30 An accumulating body of literature describes patients with CAR with antibodies reactive against retinal antigens with different molecular weights.18-23,31 These reports suggest the possibility that in the spectrum of autoimmune retinopathy that is being seen, there are a number of different retinal antigens that are involved in sensitizing the immune system. The sequence of events and the degree of pathogenicity of this putative autoimmune retinal damage need to be better studied. The absence of antirecoverin antibodies alone does not rule out the clinical diagnosis of paraneoplastic retinopathy, and screening for other antiretinal antibodies should be performed to ensure that autoimmune processes are fully assessed.31,32

There is a growing body of literature describing retinal autoimmunity in a subgroup of patients in the absence of cancer.26,27,32,33 This finding highlights the fact that paraneoplasia probably represents only 1 facet of the complex pathophysiological mechanisms that are capable of initiating autoimmune retinal damage.

Most of our patients have demonstrated greater numbers of IgM than IgG anti–retinal protein antibodies, including antibodies against recoverin. The question of patho-

![Figure 1. Case 1, a 29-year-old woman with panretinal degeneration in both eyes. Fundus photograph demonstrates marked striae of the retinae, diffuse retinal atrophy, foveal hyperpigmentation, and retinal pigment epithelial mottling of the left eye (A). A corresponding late-phase fluorescein angiogram frame shows mild retinal edema, some striae, and hyperpigmented fovea (B). A wide-angle view of the posterior pole of the right eye shows macular striae and a diffuse mottled atrophy (C). The patient had no peripheral retinal pigmented deposits.](https://www.archophthalmol.com/content/118/11/1529 franchises/REPRINTED)
genicity of IgM antiretinal antibodies will have to be evaluated further. There have been recent reports implicating IgM autoantibodies in other autoimmune disease,34-38 contrary to a previous belief that IgM autoantibodies were mainly naturally occurring and nonpathogenic.39,40 The pathogenic role of the cellular immune response in these patients was emphasized by Whitcup et al.27 They suggested that cellular immune reactivity against recoverin be used as an immunologic marker for a unique clinical entity that they labeled recoverin-associated retinopathy. The finding of a strong cellular immune response, in addition to elevated levels of antibodies against recoverin in their patient, was associated with a moderately rapid progressive retinal degeneration. In our study, we found 1 patient with elevated levels of antirecoverin antibodies in addition to strong cellular reactivity to re-

Figure 2. Case 4, seen at 47 years of age with an 8-year history of visual loss. A and B, Fundus photography demonstrates severe foveal and posterior pole cysts and retinal thickening, with mild vascular attenuation. Five years later, fundus photographs of right (C) and left (D) eyes show collapse of the cysts and continued retinal thickening from edema. Fluorescein angiography of the left eye in the early-transit phase demonstrates marked telangiectasia, an enlarged avascular zone, and early leakage throughout the posterior pole (E). A late-transit photograph of the same eye shows an enlarged foveal avascular zone in the area of the former large cyst, remnant telangiectasia, and posterior pole edema (F).
coverin (case 2), and in contrast to their findings, we encountered 2 patients with cellular reactivity to recoverin with relatively low levels of antirecoverin antibodies (cases 9 and 10).

Future research in this area should be directed to the detection and characterization of other components of the immune system, such as cytokines, which potentially may be implicated in the intricate pathogenic mechanism.

Our group of patients with retinal degeneration further emphasizes the fact that antirecoverin immunoreactivity can be found in the absence of cancer. In the absence of tumors expressing recoverin protein, the mechanism of development of antirecoverin autoimmunity in our group of patients must be explained in an alternative fashion. One of the most likely explanations for these patients’ condition is that this group of patients is prone to autoimmune disease. We frequently find that these already susceptible patients have first-degree relatives with autoimmune conditions such as lupus, rheumatoid arthritis, and fibromyalgia. If these already susceptible patients have an inflammatory insult or an eye trauma, it is possible that retinal proteins could spill into the systemic circulation, which consequently could set off an autoimmune response.

The understanding of autoimmune retinopathy is incomplete, and the pathogenic mechanisms involved in these diseases are complex. Multiple approaches to solve these questions will need to be undertaken, including animal studies, isolation of individual antibodies for study of pathogenicity, and comprehensive studies of affected
patients, before we can reach a better understanding of autoimmune pathogenesis and mechanisms.

The presence of rapid onset of visual loss in association with a panretinal degeneration, ERG abnormalities, and visual field loss should prompt the clinician to consider ordering Western blot analysis for antiretinal antibody. Patients who have positive results on Western blots should undergo further investigation with more specific laboratory tests to identify whether they have antirecoverin or other pathologic antibodies. The patient with antirecoverin antibodies should undergo evaluation for carcinoma and regular follow-up over time to ensure that an underlying carcinoma has not been missed.

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