RECOVERIN-ASSOCIATED RETINOPATHY: A CASE REPORT AND LITERATURE REVIEW

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Purpose: To report a case of recoverin-associated retinopathy.
Method: A case report.
Result: A 79-year-old woman complained of sudden blurred vision in her left eye. The corrected visual acuity was 20/20 in the right eye and 2/200 in the left eye. A fundus exam showed attenuation of the arterial vasculature and mild optic disc pallor. Optical coherence tomography revealed thinner macula thickness than that of the fellow eye. The electroretinogram demonstrated a marked decrease. Antibody testing involving Western immunoblots identified recoverin antibodies (23kDa). Serum biomarkers of autoimmune disease were negative. After a series of malignancy surveys, no hematological or solid tumor was found. Therefore, recoverin-associated retinopathy syndrome was impressed and discussed.

Conclusion: Cancer-associated retinopathy (CAR) has been documented for the past 30 years and recoverin is the most commonly implicated auto-antibody. However, recoverin-associated retinopathy is relatively rare. We offer this case, diagnosed as recoverin-associated retinopathy without malignancy, and an associated literature review.

Keywords: Recoverin-associated retinopathy, Autoimmune retinopathy, Cancer-associated retinopathy-like syndrome

INTRODUCTION

Cancer-associated retinopathy syndrome (CAR) is one type of paraneoplastic retinopathy. Paraneoplastic conditions are humorally mediated distant effects of a neoplasm. Such conditions lead to an alteration of function or destruction of remote, possibly unrelated, organs or systems. Recoverin-associated retinopathy resembles paraneoplastic retinopathy in association with serum antirecoverin antibodies but medical evaluation fails to reveal any evidence of malignancy. Here, we report a case of recoverin-associated retinopathy.

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CASE REPORT

A 79-year-old woman had poorly controlled hypertension for more than 20 years and was a secondhand smoker. She denied trauma or surgical history. Her family history includes laryngeal cancer (sister) and gastric cancer (brother and daughter).

She visited our clinic with the complaint of a sudden onset of blurred vision in her left eye. The best-corrected visual acuity was 2/200 in the left eye and 20/20 in the right eye. The intraocular pressure was within normal limits. No relative afferent papillary defect was found. Color vision test results were normal. A fundus examination showed attenuation of the arterial vasculature and mild optic disc pallor (Figure 1 upper). Fluorescein angiography showed neither perivascular leakage nor staining around the optic nerve head (Figure 1 lower). Visual field testing revealed severe constriction of the peripheral field, or so-called ring scotoma, within the central 30 degree, in both eyes. Central visual field loss was found in left poor vision eye (Figure 2). The result of optical coherence tomography showed diffuse retinal thinning in the macula area (Figure 3). Serum biomarkers for autoimmune disease, such as antinuclear antibodies, rheumatoid factor, antineutrophilic cytoplasmic antibodies, erythrocyte sedimentation rate and C-reactive protein were negative. The result of brain computed tomography was negative. Under the suspicion of CAR syndrome, we arranged an electroretinogram. The amplitude of scotopic white decreased in the left eye (Figure 4). We collected her blood to perform Western immunoblots. Testing of antibodies identified recoverin 23kDa (Figure 5), which is specific to cancer-associated retinopathy. Therefore, we performed a thorough cancer survey for hematological...
malignancies, such as lymphoma, leukemia or myeloma, and solid tumor. Abdominal sonography, mammography, upper gastrointestinal endoscopy, colon fiberoscopy, and brain and chest computed tomography scans were all performed and showed no definite evidence of cancer. Tumor markers, such as alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) carbohydrate antigen (CA)-125, and CA-199, were within normal range.

After one year follow-up, we performed Western immunoblots again and testing of antibodies still identified recoverin 23kDa. Hence, we believed the patient suffered from so-called recoverin-associated retinopathy, and we continued to observe her through regular cancer surveys. This patient has been followed up for one and half years.

**DISCUSSION**

Cancer-associated retinopathy (CAR) is a paraneoplastic disorder characterized by a progressive loss of vision, clinical signs of retinal degeneration and a reduced electroretinogram. Similar to other paraneoplastic disorders, cancer-associated retinopathy is most often associated with an underlying small-cell carcinoma of the lung.¹ Recoverin is thought to be the most frequently implicated antigen in patients with CAR.²,³

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**Figure 2** Visual field testing appeared severe constriction of the peripheral field, so-called ring scotoma, within the central 30 degrees, in both eyes. Central visual field loss was found in left poor vision eye.

**Figure 3** Optical coherence tomography appeared thinning of the whole layer in left eye.
Recoverin, a member of the calmodulin family, is a Ca^{2+}-dependent activator of photoreceptor guanylate cyclase involved in light and dark adaptation of photoreceptors by regulation of rhodopain phosphorylation. The calcium-binding domains of recoverin appear central to the autoimmune reaction in CAR. Recoverin is localized to chromosome 17p13.1, a region rich with cancer-related loci including p53.

Our patient presented retinal disease similar to cancer-associated retinopathy and had rapidly progressive loss of vision with clinical signs of a retinal degeneration, extinguished electroretinogram and elevated serum levels of antibodies against recoverin. However, despite one and half years of follow-up, no evidence of an underlying malignancy has been obtained. These findings, as well as those of Whitcup et al and Heckenlively et al, have revealed another group of patients with retinal degeneration who have antirecoverin autoimmunity without cancer therefore, giving the impression of recoverin-associated retinopathy.

The initial description of recoverin-associated retinopathy was published in 1998 by Whitcup et al. They described four patients with recoverin but without cancer found. They demonstrated those diseases to be immunologically distinct from those of patients with other retinal degenerations or uveitis, and proposed that this condition be referred to as recoverin-associated retinopathy.

In the past, antirecoverin antibodies were considered to be specific markers of CAR. However, in 2000, Heckenlively et al collected blood samples of 521 patients with retinal degeneration and no medical history of cancer. Ten patients were found to have recoverin, and then were requested to undergo evaluation to rule out carcinoma. After an extensive medical survey, no malignancy was found. The findings of the above study as well as those of Whitcup et al have revealed another group of patients with retinal degeneration who have antirecoverin autoimmunity without cancer. These patients present a diagnostic dilemma for clinicians, since they are difficult to distinguish from patients with CAR, both clinically and using laboratory studies.

For patients suspected to have CAR without a
known malignancy, Raj K Maturi, MD recommended a chest radiograph be obtained. If the result is normal, a CT scan of the chest is appropriate. Additional imaging studies for a possible primary neoplasm include CT of the abdomen and pelvis, mammography (for woman), and total-body positron-emission tomography (PET) or CT/PET. Complete physical examination, including pelvic and breast examinations for women, is also recommended.

The National Comprehensive Cancer Network (NCCN) released the latest guidelines for occult primary cancer surveys in 2013 (Figure 6). They recommend complete history and physical examination, including breast, genitourinary, pelvic, and rectal exams, with review of past biopsies or malignancies, removed lesions, spontaneously regressing lesions, and existing imaging studies. Since our patient had history of uterine myoma and received abdominal total hysterectomy, the pathology report was negative for malignancy. Moreover, complete blood count, electrolytes, liver function tests, creatinine, calcium, chest/abdominal/pelvic CT scan, hemoccult, and symptom directed endoscopy are also important.

The role of the longitudinal monitoring of serum anti-retinal antibody levels is not well established, and routine use may be technically difficult and cost-prohibitive. Yet, elevation of serum antibody levels may occur long after the treatment of primary cancer and may be associated with progression of CAR; the quantification of serum anti-retinal antibody levels may trigger reinstatement of immune therapy or guide changes in treatment strategies in some cases. Importantly, fluctuations in serum auto-antibody levels, while correlating to CAR activity, are typically not associated with cancer recurrence or progression.

The mechanism underlying the presence of circulating antirecoverin antibodies in recoverin-associated retinopathy is unknown. In patients with cancer-associated retinopathy, antirecoverin antibodies are thought to result from antibodies directed against tumor antigens that also recognize recoverin. This theory has been validated in reports in which 3 patients with CAR syndrome and positive antirecoverin antibodies demonstrated recoverin proteins in their malignant tumors.

Perhaps our patient had an underlying recoverin-positive malignancy that was cured by an immune response mounted against the tumor, leaving her with the antirecoverin response and secondary retinopathy. One could also hypothesize an immune response directed against an infectious agent cross-reacted with recoverin. Although the understanding of recoverin-associated retinopathy is incomplete, and the pathogenic mechanisms involved in these diseases are complex, it appears immune response against recoverin is associated with severe retinal degeneration and vision loss.

The differential diagnoses include retinitis pigmentosa, systemic autoimmune disorder, and trauma. Patients with recoverin-associated retinopathy differ from those with typical RP in that they seldom have pigmentary deposits. Furthermore, for such patients the recent onset of unexplained visual loss often progresses at a more rapid rate than in case of typical RP. Hecken-
lively et al. found their patients frequently had first-degree relatives with autoimmune conditions such as lupus, rheumatoid arthritis, and fibromyalgia. However, ANA positive patients account for only 1 in 10 of those with recoverin-associated retinopathy. If these already susceptible patients have an inflammatory insult or eye trauma, it is possible that retinal proteins could spill into systemic circulation.7

The presence of rapid onset of visual loss in association with panretinal degeneration, ERG abnormalities, and visual field loss should prompt clinicians to consider ordering Western blot analysis for antirecoverin or other pathologic antibodies. Since CAR can precede oncologic diagnosis by several months16, patients with antirecoverin antibodies should undergo evaluation for carcinoma and regular follow-up over time to ensure an underlying carcinoma has not been missed.

REFERENCE

8. Raj KM, Cancer Associated and Related Autoimmune Retinopathies. Updated: Jun 20, 2012 (Medscape)
目的：報告一例 Recoverin 抗體相關之視網膜病變及文獻回顧。

方法：病例報告。

結果：這位 79 歲女性來門診時抱怨突發性左眼視力模糊，矯正後最佳視力左眼 2/200，右眼 20/20。眼底檢查僅發現視網膜小動脈略狹窄，視神經盤輕微蒼白，視野檢查顯示兩眼中央三十度內週邊嚴重損失，視野較差之左眼出現中央視野喪失。光學同調斷層掃描儀發現左眼黃斑部厚度較薄，視網膜電圖訊號明顯衰退，西方墨點免疫染色血液檢查發現 Recoverin 抗體。目前未發現癌症病兆，所以診斷病人为 Recoverin 抗體相關之視網膜病變。

結論：根據文獻，癌症相關之視網膜病變被證實和 Recoverin 等抗體有關，許多案例在過去三十年已被提出並廣泛被接受。此病人臨床表現類似癌症相關之視網膜病變，也發現 Recoverin 抗體，但追蹤一年半來未診斷任何癌症病兆，過去文獻也曾發表過類似案例，但相對數量較少，因此提出此案例並做文獻回顧。