Patients with systemic cancer may have a variety of ocular complaints. Most commonly these are metastases or adverse effects of therapy. Paraneoplastic syndromes, like cancer-associated retinopathy, rarely cause ophthalmic symptoms. We describe a patient with a malignant mixed müllerian tumor and cancer-associated retinopathy who had circulating serum antibodies to recoverin and cells positive for recoverin in the tumor. We discuss the typical clinical symptoms as well as the pathophysiology of this uncommon disorder.


A 60-year-old white woman arrived in the emergency department complaining of 3 weeks of progressive, painless dimming of her vision and swirling flashes of light. Further history revealed 8 months of postmenopausal bleeding with associated malaise, weight loss, and anorexia. On physical examination the emergency department physician found a large, firm, uterine mass similar in size to an 18-week pregnancy. An abdominal computed tomographic scan demonstrated the uterine mass, diffuse adenopathy, and hepatic lesions consistent with metastases. A transvaginal endometrial biopsy revealed a malignant mixed müllerian tumor.

The paraneoplastic syndromes, like cancer-associated retinopathy (CAR), are the least common cause of visual dysfunction in patients with neoplasms. Cancer-associated retinopathy is characterized by painless and progressive visual loss, photopsias, ring scotoma, and loss of rod and cone function as demonstrated by electroretinography due to the production of autoantibodies against retinal antigens stimulated by a systemic, nonocular tumor. Since its first description in 1976, CAR has become an increasingly recognized phenomenon. The following clinical and pathologic presentation of a malignant mixed müllerian tumor causing severe visual dysfunction illustrates this rare disorder.
vision separated by a midperipheral ring scotoma (Figure 2). Suspecting a diagnosis of CAR, electroretinography and serum 23-kd antibodies (anti-recoverin) were ordered. The electroretinogram showed no rod function and minimal cone function (Figure 3). The patient’s 23-kd antibody titer was strongly positive to a dilution of approximately 1:3200 (oral communication, Charles Thirkill, PhD, 1998).

She was treated with palliative radiation for her cancer and oral prednisone for the CAR. After 3 days of oral prednisone, she noted significant improvement of her vision. She stated she could better recognize faces, more easily walk down stairs, and had improved ability to read. She maintained a visual acuity of 20/30 OU until her death 6
months later, at which time an autopsy was performed.

**HISTOPATHOLOGIC FINDINGS**

The patient's globes were removed a few days post mortem and autolysis was evident. Hematoxylin-eosin-stained sections through the globe demonstrated nearly complete loss of photoreceptor outer and inner segments, as well as the outer nuclear layer in the retina (Figure 4). A small island of cone inner segments and cell bodies was identified in the central macula. Of interest, a few areas of the choriocapillaris demonstrated mononuclear inflammatory cells consistent with lymphocytes extending into the photoreceptor layer of the retina. The peripheral retina also contained rare areas of lymphocytes. Immunohistochemistry confirmed a mixed population of B and T lymphocytes in these areas. The remainder of the inner retina was intact. Occasional drusen were noted along Bruch's membrane. Results of an examination of the anterior segment and optic nerve were unremarkable.

Hematoxylin-eosin staining of the original endometrial biopsy specimen revealed sheets of poorly differentiated cells with marked nuclear pleomorphism, abundant mitotic figures, and no glandular differentiation (Figure 5, left). Large areas of necrosis and hemorrhage were present. In addition, a distinct focus of well-differentiated adenocarcinoma was noted in a fragment separate from the poorly differentiated cells (Figure 5, right). To determine the histogenesis of the poorly differentiated foci, immunohistochemical stains were performed with the following antibodies using the avidin-biotin method6: pancytokeratin (dilution 1:25; Vector Laboratories, Burlingame, Calif) and cytokeratin AE 1-3 (dilution 1:80; Boehringer Manheim, Indianapolis, Ind). The poorly differentiated cells failed to stain with either keratin antibody, with appropriate positive and negative controls. The final diagnosis was a mixed sarcoma and carcinoma (mixed malignant mullerian tumor).

A sample of the patient's uterine tumor was also obtained post mortem. Frozen sections were processed for immunofluorescence with rabbit anti-recoverin antibody (1:500; provided by A. S. Polans, PhD, University of Wisconsin, Madison) and secondary anti-rabbit IgG labeled with Cy-3 (1:50; Jackson Immunoresearch Laboratories, West Grove, Pa). Sections processed with anti-recoverin antibody (Figure 6, left) showed strong fluorescence of scattered tumor cells surrounded by

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Figure 4. Examination of the retina (left, low power; right, high power) at the time of autopsy found loss of the retinal outer nuclear and photoreceptor layers (black arrow). Also present are inflammatory cells (open arrow) (hematoxylin-eosin, original magnification ×50 [left] and ×200 [right]).

Figure 5. Endometrial biopsy of the uterus showed poorly differentiated cells most consistent with sarcoma (left) and a focus of well-differentiated adenocarcinoma (right) (hematoxylin-eosin, original magnification ×200 [left] and ×400 [right]).
bodies to a 23-kd retinal protein, were initially found to have anti-lung, a patient with endometrial carcinoma has most commonly been associated with small cell carcinoma of the lung, but case reports exist linking this entity to other carcinomas. Patients with CAR were initially found to have antibodies to a 23-kd retinal protein, later identified as recoverin. Recoverin is a retinal photoreceptor calcium-binding protein that is involved in light and dark adaptation through the regulation of rhodopsin phosphorylation. However, our histopathologic findings, as well as those of others, demonstrated inflammatory infiltrates in the eyes of patients with CAR. Further, other cases have included the presence of an active vitritis. Most likely these are secondary cellular response to the initial humoral response, but nonetheless both mechanisms may play some role in the process.

Cancer-associated retinopathy has most commonly been associated with small cell carcinoma of the lung, cervical, ovarian, and breast carcinomas have all been reported in patients with CAR. Of note, 50% of patients have retinopathy as the first manifestation of their underlying neoplasm.

An unanswered issue is what type of immune reaction, humoral or cellular, leads to photoreceptor destruction. Most of the evidence points to a humoral mechanism as anti-recoverin antibodies are found in the serum of patients with CAR and anti-recoverin antibodies have been shown to induce photoreceptor apoptosis. Further, in the past decade a variety of autoantibodies to retinal antigens have also been reported, although the 23-kd antibody against recoverin is the most common. However, our histopathologic findings, as well as those of others, demonstrated inflammatory infiltrates in the eyes of patients with CAR. Further, other cases have included the presence of an active vitritis. Most likely these are secondary cellular response to the initial humoral response, but nonetheless both mechanisms may play some role in the process.

The presentation of CAR typically involves a few key symptoms. First, patients report dimming of their vision occurring over days to weeks. Second, they also complain of acute-onset nyctalopia. Finally, patients often describe positive visual symptoms such as swirling and flashing lights.

On examination, patients have decreased acuity, diminished color vision, and ring scotoma visual field defects. The posterior segment of the eye can appear totally normal, but occasionally there is a mild inflammatory reaction in the vitreous and the retinal vasculature is attenuated. The electroretinogram, a test of retinal function, is markedly reduced. Serum antibody testing may confirm the diagnosis. Histopathology of the retina demonstrates loss of the photoreceptors.

Treatment for CAR involves modulation of the immune system to reduce the autoimmune response. The most widely reported therapy consists of 250 mg of intravenous methylprednisolone 4 times daily or 60 to 80 mg of oral prednisone daily, followed by a slow taper to a low maintenance dose. Other options being investigated include intravenous immunoglobulin and plasmapheresis. Most recently, Tolpa Torf preparation (Tolpa Norway Ltd, Honefoss, Norway), a naturally occurring immunomodulator, has been shown to be effective in reducing antibody levels.

Overall, the clinical course of CAR is one of deterioration. Patients typically experience progressive visual loss, worsening of their visual field defects, and flattening of their electroretinogram. Despite this grim prognosis for visual function, patients who receive adequate treatment may maintain useful vision until the time of death. Overall survival depends on the underlying tumor and its staging at diagnosis.

Figure 6. Left, Tumor cells processed with anti-recoverin antibodies show strongly positive tumor cells surrounded by unlabeled cells. Right, Tumor cells processed with nonimmune rabbit serum show weak background fluorescence (original magnification ×100).

Cancer-associated retinopathy is a rare paraneoplastic process in which antibodies are thought to be formed against a protein produced by the tumor that has homology to specific retinal proteins. Patients with CAR were initially found to have antibodies to a 23-kd retinal protein, later identified as recoverin. Recoverin is a retinal photoreceptor calcium-binding protein that is involved in light and dark adaptation through the regulation of rhodopsin phosphorylation. However, our histopathologic findings, as well as those of others, demonstrated inflammatory infiltrates in the eyes of patients with CAR. Further, other cases have included the presence of an active vitritis. Most likely these are secondary cellular response to the initial humoral response, but nonetheless both mechanisms may play some role in the process.

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