An Unusual Type of Cancer-associated Retinopathy in a Patient with Ovarian Cancer

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We studied a case of unusual retinopathy in a 35-year-old woman who presented with bilateral visual deterioration due to retinal pigmentary mottling and serous elevation in the posterior pole. Two years before, she had undergone hysterectomy and bilateral salpingo-oophorectomy for ovarian cancer. Her electroretinogram became subnormal, and her fluorescein angiogram exhibited multiple deep retinal pigment epithelial leakages and subretinal dye pooling in both eyes. Corticosteroid therapy failed to prevent visual loss. She was found to possess antibodies against retinal 45 kd protein. This led to a diagnosis of cancer-associated retinopathy with atypical protein profile. We report a rare variety of cancer-associated retinopathy in a patient with ovarian cancer.

Key words: cancer-associated retinopathy, paraneoplastic syndrome, autoantibody, ovarian cancer

INTRODUCTION

Cancer-associated retinopathy (CAR) is a type of paraneoplastic syndrome, which is caused by the remote effects of a cancer without direct invasion or metastasis.1-3 Possible immune cross-reactivity between antigens in the cancerous tissue and antigens in the retina may play an important role in its pathogenesis. 23 kd CAR syndrome is its typical form, and it is generally encountered in association with small-cell carcinoma of the lung.3

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We report on a patient who developed an unusual form of paraneoplastic retinopathy in connection with ovarian carcinoma.

CASE REPORT

In February 1997, a 35-year-old woman was referred to us with a chief complaint of visual blurriness and a sense of darkness in both eyes for one month. In February 1995, she had undergone surgery (total hysterecomy with bilateral salpingo-oophorectomy) for ovarian serous carcinoma and endometrial carcinoma stage IIa. In January 1997, the patient was found to have a recurrence of the adenocarcinoma in the posterior abdominal cavity. No distant metastasis was detected. She was admitted to receive chemotherapy with dexamethasone, cisplatin and taxol.

The initial examination showed mildly deteriorat-
ed visual acuity. The patient’s best-corrected visual acuity was R.E.:20/25 and L.E.: 20/30. Her pupils were isocoric and prompt to slightly sluggish to light, but there was no afferent pupillary defect. Ocular motility, slit-lamp examination findings, and intraocular pressure were normal. An area of localized subretinal fluid in the posterior pole surrounded by leopard skin-like alterations of the retinal pigment epithelium was observed in both eyes (Figure 1 A, B). Fluorescein angiography, performed in April 1997 when her vision had decreased to 20/40 in both eyes, showed early patchy hyperfluorescence caused by retinal pigment epithelial leakages and late dye pooling in the subretinal space (Figure 1 C, D). No obvious thickening of the choroid could be detected in either eye by ultrasonography. Electroretinography revealed a bilateral decrease of b-waves under both photopic and scotopic conditions (Figure 2).

Results of Western blot analysis of the patient’s blood revealed the presence of antibodies to 45 kd retinal protein with a titer of 1:1000 (Figure 3, lane B). On the basis of her clinical signs and the immunological findings, CAR was diagnosed. By May 1997, her vision had continued to deteriorate to 20/50 in both eyes. Prednisolone, 50 mg P.O. daily, was tapered down over a four week period. Her ocular condition appeared to be stabilized temporarily, however, it gradually deteriorated in spite of therapy. In July 1997, her visual acuity decreased to OD: 20/100, OS 20/80. Her electroretinogram became extinguished, and an electrooculogram also showed subnormal results (Figure 2). Funduscopy findings showed more prominent pigmentary mottling and persistent shallow serous elevation (Figure 1 E-H). She was lost to follow-up until three months later when she was re-hospitalized due to recurrence of the carcinoma. Her vision at that time was so poor that she could only perceive movement of objects. Ophthalmic examination and further testing were not performed at this time due to the patient’s strong refusal. The patient died of systemic complications three weeks later.

**DISCUSSION**

Visual paraneoplastic syndromes, often leading to loss of vision, may result as remote effects of cancer. It has been proposed that tumors release antigens into the circulatory system, resulting in a high titer of antibodies that are able to penetrate the blood-retina barrier, and then cross-react with susceptible retinal cells. CAR, the most well known of these syndromes, affects photoreceptors. Melanoma-associated retinopathy (MAR) is thought to affect bipolar cell function, and bilateral diffuse uveal melanocytic proliferation (BDUMP) targets the uveal tract. These syndromes have been observed most often with small cell carcinoma of the lung yet other carcinomas, such as cervical, ovarian, and breast, may cause these effects. In addition, Mizener et al. reported two similar cases of retinopathy in patients without any sign of cancer, and raised the possibility that this interesting autoimmune retinopathy may also occur independently of cancer.

While 23 kd retinal protein is designated as the CAR antigen since small-cell lung carcinoma (SCCL)-related CAR consistently produces antibodies against 23 kd protein, other proteins have been identified in SCCL- or other malignancy-related paraneoplastic syndromes. Adamus reported autoantibodies to a retinal protein of 46 kd molecular weight (retinal enolase), Grunwald of 65 kd and 23 kd, Suzuki of 62 kd protein, Murphy of 60 kd in patients with small cell carcinoma of the lung, and Okawa of 34 kd in patient with endometrial cancer.

Serum from our patient did not react against any previously described retina antigens, but did positively react against an antigen with a molecular weight of 45 kd, which as yet remains unidentified. The absence of reactivity with the previously described 23 kd retinal antigen usually associated

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**Fig. 1(A-H).** A-D. Fundus photographs of the left (A) and right (B) eyes, taken in March 1997. Diffuse pigment mottling and serous retinal detachments were noted at both posterior poles. Fluorescein angiography of (the) right eye showing early patchy hyperfluorescent spots (C) and late pooling of the dye in the subretinal space (D). E-H. Three months later, funduscopy findings of left (E) and right (F) eyes and fluorescein angiographic findings of (the) right eye (G,H) showed rapid deterioration during the interval.
March

Fig. 2. Serial Electoretinographic (electroretinographic) recordings during 4 (taken over a four) month-period, showing the progressive decrease in the amplitudes of a- and b-wave(s) in (under) both scotopic and photopic conditions. Electrooculogram also showed the decrease in Arden ratio in her both eyes. (An electrooculogram also showed a decrease in the Arden ratio in both eyes.)

with the CAR syndrome does not exclude the diagnosis of paraneoplastic retinopathy in patients fitting the clinical profile of this disease.

The most common ocular findings in CAR include narrowed retinal arterioles, abnormal retinal pigmentation, epithelial mottling, and optic disc pallor.\textsuperscript{13} Compared to the previously reported cases, the alteration of the retinal pigment epithelium was far more prominent in our case, and was quite striking on the fluorescein angiogram. Brink et al\textsuperscript{14} reported similar pictures including the areas of subretinal fluid in the posterior poles and localized exudative retinal detachments in both eyes.

The ERG is always markedly reduced or absent in both photopic and scotopic settings and firmly establishes the diagnosis of CAR syndrome.

Consistently, our patient showed a progressive decrease in electroretinographic response and in the Arden ratio of electrooculography.

Some authors have noted improvement in visual function with the use of steroids,\textsuperscript{15} whereas others have not.\textsuperscript{10,12} Most agree that treatment of the primary malignancy alone does not improve vision. Our patient gained a temporary stabilization in vision with the use of systemic steroids in combination with chemotherapy directed at the recurrent pelvic cavity cancer. However, her vision did eventually deteriorate, suggesting that once widespread photoreceptor degeneration has occurred, therapy is no longer likely to be of benefit.

We believe we have presented a patient with a rare variety of cancer-associated retinopathy associ-
Fig. 3. Western blot analysis of the reaction of the patient's serum (lane B) diluted 1:1000 with bovine retina fractions. Note the sharp reaction in the range of 45 kd. Other lanes are of various molecular weight markers, serum from a normal human (lane A), a patient with lymphoma-associated retinopathy (lane C), a patient with breast cancer-associated retinopathy (lane D), a patient with melanoma-associated retinopathy (lane E), and a patient with small cell carcinoma-associated retinopathy with the 23 kd photoreceptor component (lane F).

References