Cancer-Associated Retinopathy during Treatment for Small-Cell Lung Carcinoma

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A 70-year-old woman with small-cell lung carcinoma (c-T4N2M0) was treated by six courses of combination chemotherapy (carboplatin and etoposide). After two weeks, she complained of a sense of darkness and night blindness. A Western blot analysis showed that the patient’s serum bound with the recombinant 23-kDa retinal cancer-associated retinopathy (CAR) antigen at 1:1,000 dilution. Her visual acuity became so poor that she could only recognise a hand motion at 50 cm despite treatment with corticosteroids and combination chemotherapy. The patient was diagnosed as having a rare type of CAR because CAR is usually found before the diagnosis of primary cancer.

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Key words: visual loss, paraneoplastic syndrome, retinal degeneration, cancer-associated retinopathy (CAR) antigen, recoverin, prednisolone

Introduction

Cancer-associated retinopathy (CAR), which was first reported by Sawyer et al (1) in 1976, is one of the paraneoplastic syndromes which are a remote effect of systemic cancer. CAR is associated with epithelial neoplasm, mostly small-cell lung carcinoma and is characterized by the degeneration of retinal photoreceptors (2-11). A photoreceptor protein, recoverin, has been recognized as the autoantigen of this disorder (12-17). It has been reported that CAR is usually found before the diagnosis of primary cancer, but there have been some reports that this disorder occurred during the treatment of malignant diseases (9, 18, 19). This report describes a 70-year-old woman with small-cell lung carcinoma who had rapidly progressive visual loss in both eyes during a period of one month.

Case Report

A 70-year-old woman had complete response of small-cell lung carcinoma (c-T4N2MO) for eleven months with five courses of combination chemotherapy consisting of carboplatin (400 mg/m² for one day) and etoposide (100 mg/m² for three days). A roentgenogram of the chest revealed a tumor in the left middle lung field and a relapse of the hilar and mediastinal lymphadenopathy (Fig. 1) and she was admitted in July 1997. On admission, her body temperature was 36.2°C, heart rate 68 beat/min, respiratory rate 15/min, and blood pressure 158/80 mmHg. Arterial blood gas analysis revealed slight hypoxemia (pH 7.40, partial pressure of oxygen; PaO₂ 65.4 Torr, partial pressure of carbon dioxide; PaCO₂ 42.0 Torr, HCO₃⁻ 25.2 mmol/l). Laboratory data revealed a white blood cell count of 4,700/mm³, red blood cell count 337×10⁴/mm³, hemoglobin 10.8 g/dl, platelet count 14.8×10⁴/mm³, aspartate aminotransferase 23 U/l, alanine aminotransferase 10 U/l, lactate dehydrogenase 631 U/l, alkaline phosphatase 274 U/l, C-reactive protein 0.11 mg/dl. Serum neuron-specific enolase (NSE) and pro-gastrin releasing peptide (pro-GRP) levels were 21 ng/ml and 853 pg/ml.

Two weeks after a sixth course of combination chemotherapy (same regimens), she complained of a sense of darkness, shimmering lights surrounding her visual fields and night blindness. There was no family history of visual problems, including retinitis pigmentosa. Visual acuity in the right and left eyes was 0.2 and 0.1. Goldmann perimetry showed extremely constricted visual fields in both eyes, a paracentral scotoma and an enlargement of the blind spot of Mariotte in the right eye (Fig. 2). Critical flicker fusion frequencies (CFF) in right and left eyes were 12 and 19 Hz (normal range>35 Hz). Her pupils were isocoric and sluggish in response to light, but there was no afferent pupillary defect. Slit-lamp examination showed in-
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Figure 1. A roentgenogram of the chest revealed a tumor in left middle lung field and a relapse of the hilar and mediastinal lymphadenopathy.

Inflammatory cells in the anterior chamber and intraocular pressures were normal. Fundus examination showed a mild narrowing of the retinal blood vessels and slight pallor of both optic disks (Fig. 3). Indocyanine green angiography revealed a patchily stained area and narrowed arteries in both eyes (Fig. 4). Electroretinogram (ERG) was non-recordable. A computed tomogram (CT) and magnetic resonance image (MRI) of the brain and orbit showed no abnormal findings. Laboratory findings, including serum titers for herpes simplex virus, varicella-zoster virus and cytomegalovirus, were normal.

Over the subsequent two weeks, her vision continued to deteriorate in both eyes. Color vision was severely reduced. A neuro-ophtalmologic examination revealed the visual acuity in the right eye to be 0.05 and in the left eye to be a hand motion at 50 cm, with no change in the ERG. A progressive narrowing of the retinal arteries was found on fundus examination and indocyanine green angiography. A Western blot analysis showed that the patient’s serum bound with the recombinant 23-kDa retinal CAR antigen at 1:1,000 dilution (Fig. 5). On the basis of her clinical signs and neuro-ophtalmologic examination findings, CAR was diagnosed.

The patient was given 1,000 mg of methylprednisolone intravenously for three days and started on 40 mg prednisolone per day, which was tapered to 5 mg per week. Plasmapheresis has not been done. She had a temporary improvement of vision for one month, but her vision in both eyes deteriorated due to the advance of the cancer. Although she has been treated with combination chemotherapy (carboplatin and etoposide), her visual acuity in both eyes became to be a hand motion at 50 cm.

Discussion

Disorders of the retina, which often lead to the loss of vision and may result as a remote effect of cancer, have been termed visual paraneoplastic syndrome or CAR. In this syndrome, the nervous system is not invaded by primary or metastatic lesions. Although a variety of cancers can be involved, including endometrial cancer (18–20), cancer of the cervix uteri
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Figure 3. Fundus examination showed a mild narrowing of the retinal blood vessels and slight pallor of both optic disks in both eyes.

Figure 4. Indocyanine green angiography revealed a patchily stained area (arrowhead) and narrowed arteries in both eyes.

Figure 5. A Western blot analysis showed that the patient's serum bound with the recombinant 23-kDa retinal CAR antigen at 1:1,000 dilution (arrowhead). PC: positive control.

(3) and cutaneous malignant melanoma (21, 22), CAR is most frequently associated with small-cell lung carcinoma (2–11, 23). The incidence of CAR in each patient with various types of cancer is not clear because this disease has not been looked for in most reported oncological series (23). The clinical triad of CAR was photosensitivity, ring scotomatous visual loss and attenuated retinal arteriole caliber (24). A high frequency of night blindness and color loss has been reported in this disease (7). However, it has been most frequently reported that the initial complaint in patients with CAR is visual loss. Slit-lamp examination showed inflammatory cells in the anterior chamber or the vitreous body (7, 8, 10), and visual field examination showed central scotoma, ring scotoma or overall moderate to severe depression. Fundus examination showed non-specific pigment mottling in the posterior pole and vascular at-

tenuation with variable sheathing (23). In addition, it has been reported that optic discs in CAR patients show mild pallor (7, 11, 24). With regard to the optic disc pallor, chemotherapeutic agent-induced optic neuropathy should be considered in the differential diagnosis in the case which has the occurrence of visual loss during chemotherapy, if the presence of CAR antigen is not detected.

Although the biologic mechanisms of paraneoplastic degenerative retinopathy have not been fully defined, the presence of specific antibodies in patients with CAR suggest autoimmunity as a contributing factor (2, 25). Thirkill et al (4) reported on the isolation of an autoantibody which reacts strongly with the 23-kDa retinal protein, recoverin. This protein is a member of the E-F hand family of calcium-binding proteins involved in the transduction of light by vertebrate photoreceptors and is also identified as an autoantigen in CAR (12, 13). It has been reported that this photoreceptor-specific protein is expressed by the tumor in CAR patients (16) and by a human lung cancer cell line (MN-1112), which was established from tumors of small-cell lung carcinoma patients with CAR (17, 26). In addition, expression of recoverin was not found in patients with diabetic retinopathy, age-related macular degeneration and in small-cell lung carcinoma patients without CAR (7, 17). On the other hand, Adamus et al reported serum antibodies to a 46 kDa protein in CAR patients with various types of cancer and that protein sequence analysis of the peptides from the protein revealed a high homology with human enolase, an important glycolytic enzyme (27). We did not evaluate the 46 kDa protein in the present case. It has been hypothesized that an immunological cross-reaction between tumor antigens and specific retinal components, recoverin or enolase, is responsible for the induction of the unique autoantibody response in patients with CAR (2, 15).

It has been reported that there are some autoantibodies in
paraneoplastic neuropathy other than CAR. In patients with paraneoplastic sensory neuropathy (28) or paraneoplastic cerebral degeneration (29), a polyclonal complement-fixing immunoglobulin G (IgG) antibody (anti-Hu) or anti-Purkinje cell antibodies are found in the serum and cerebrospinal fluid. We did not evaluate those antibodies because our patient had no paresthesia, dysesthesia or cerebellar ataxia.

CAR is generally found before diagnosis of the underlying primary cancer (2–8, 10, 11). This remote effect of cancer on the eye should be recognized as a presenting sign of previously undiagnosed malignant disease. There are some reports stating that CAR has developed in patients undergoing treatment for malignant disease including small-cell lung carcinoma (9, 18, 19). In the present case, there was an 11-month interval from the diagnosis of lung cancer to the onset of CAR. It has been reported that the interval is 9 to 21 months (9, 18, 19). In addition, CAR was accompanied by progression of malignant diseases in two of three cases (18, 19), as in the present case. Although the presence of CAR is not predictive of advanced or aggressive malignancy (30), the onset of this syndrome during the treatment of malignancy may be related to the advance of malignant diseases.

The treatment for CAR is immunosuppression with corticosteroids. It has been reported that CAR patients attain a temporary improvement in vision following the administration of prednisolone (5, 11, 24). But the optimal dose of prednisolone dose is not known. A systemic response of the malignant diseases to chemotherapy or radiation has not correlated with improvement in visual function (5, 30). In the present case, administration of prednisolone induced a temporary improvement of her visual impairment, but chemotherapy did not. Plasmapheresis was reported to have reduced the autoantibody titers, but did not benefit the patient’s declining vision, because of irreversible cell damage (4).

CAR has been mainly reported by ophthalmologists because these patients have visual loss before the underlying malignancy is diagnosed. However, in some patients, CAR appeared during treatment for lung cancer as in the present case. It is important that in the case of visual loss, not only brain metastasis from primary cancer or drug-induced retinopathy but also CAR is considered.

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References

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