Treatment of Paraneoplastic Visual Loss With Intravenous Immunoglobulin

Report of 3 Cases

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**Background:** Paraneoplastic visual loss is an autoimmune disorder believed to be caused by the remote effects of cancer on the retina (cancer-associated retinopathy [CAR]) or optic nerve. Both disorders may result in rapid and complete blindness. Spontaneous recovery of vision has not been reported. The serum of patients with CAR contains autoantibodies against recoverin, enolase, or unidentified retinal proteins. Autopsy examination results of eyes of blind patients with CAR show complete absence of the retinal neurons involved in phototransduction. Corticosteroids and plasmapheresis are the only treatment options previously described.

**Objective:** To treat paraneoplastic visual loss.

**Design and Methods:** Three patients with metastatic cancer developed rapidly progressive loss of vision. The first patient had visual acuity of hand movements in each eye before intravenous immunoglobulin treatment. The second patient had visual acuity of light perception in both eyes. The third patient's visual acuity was 20/400 OD and 20/20 OS. Diagnostic tests included magnetic resonance imaging of the head and cytologic examination of the cerebrospinal fluid to exclude metastasis as the cause of visual loss and then an electroretinogram and serum tests for autoantibodies against retinal antigens to confirm the clinical diagnosis of CAR. Patients 1 and 2 were treated with intravenous immunoglobulin (400 mg/kg per day) for 5 days; however, patient 3 received only a single dose due to adverse effects consisting of shortness of breath and itching.

**Results:** Within 24 hours of taking the first dose of intravenous immunoglobulin, the visual acuity of patient 1 improved from hand movements only in both eyes to 20/50 OD and 20/200 OS. After the third day of treatment, visual acuity in the left eye further improved to 20/40. Even with the improved acuity, Goldmann visual field perimetry results showed poor responses in both eyes. However, 2 weeks later there was marked visual field improvement, and visual acuity was maintained at 20/50 OD and 20/40 OS. Patient 2 had no improvements and continued to have light perception in both eyes. Patient 3 had improvements in visual field defects but remained 20/400 OD and 20/20 OS.

**Conclusion:** Intravenous immunoglobulin may be another treatment option offered to patients with paraneoplastic visual loss in addition to corticosteroids or plasmapheresis because a review of the medical literature has shown no spontaneous improvements of visual function without treatment.


PARANEOPLASTIC visual loss caused by the remote effects of carcinoma was described by Sawyer and associates more than 20 years ago. In this disorder, visual function deteriorates rapidly, often within weeks to months and sometimes within days. Diagnosis of cancer-associated retinopathy (CAR) is made by exclusion of metastasis and radionecrosis as causes of visual loss, an attenuated response to light flashes on the electroretinogram (ERG), and detection of autoantibodies against retinal cell antigens. Results of histopathologic examination of autopsied eyes show degeneration of the retinal neurons involved in phototransduction.

Treatment of the visual loss caused by this disorder often has been disappointing. Use of systemic corticosteroids has been reported to improve and maintain visual function. In our research (J.G. and N.A., unpublished data, 1998) and that of others, corticosteroid therapy has been ineffective. Consequently, we sought an alternative therapeutic option. Review of treatments for central nervous system paraneoplastic disorders has shown that intravenous immunoglobulin (IVIg) completely reversed paraneoplastic cerebellar degeneration. To our knowledge, the role of IVIg in CAR treatment has not been explored. We report our results in 2 patients with CAR and 1 patient with paraneoplastic optic neuritis who were treated with IVIg, and compare them with a comprehensive literature review of patients with untreated CAR and those who received corticosteroids or plasmapheresis.
MATERIALS AND METHODS

Human retinal protein extracts were solubilized in sodium dodecyl sulfate gel loading buffer, separated on 12% slab gels, and then transferred to polyvinylidene fluoride membranes for immunostaining.

Non-specific binding sites were blocked by incubating the blots with 10% normal goat serum, 1% bovine serum albumin in 10 mmol phosphate-buffered saline solution (pH 7.2). The blots were incubated with the patients’ serum samples diluted 1:200 in 10 mmol phosphate-buffered saline solution with 1% bovine serum albumin. Antihuman alkaline phosphatase secondary antibodies were used in a 1:4000 dilution.

Color was developed using a phosphatase substrate kit (BCIP/NBT kit; Zymed, San Francisco, Calif). In controlled experiments, human serum samples from healthy donors were used. Dot blot methods using recombinant human recoverin or purified bovine enolase were used to confirm the specificity of antirecoverin or antienolase labeling. Rabbit antiserum raised against biochemically purified bovine enolase were used to confirm the specificity of antirecoverin or antienolase labeling. Rabbit antiserum raised against biochemically purified bovine enolase or recoverin was used as a control for positive labeling.

REPORT OF CASES

CASE 1

A 62-year-old woman with stage IV adenocarcinoma of the lung was admitted to the medical service on May 10, 1996, for evaluation of 3 days of rapidly progressive visual loss. In April 1993, she had a left lower lobe wedge resection of the lung and resection of a solitary right-sided parietal brain metastasis with postoperative cranial irradiation. A recent workup for back pain uncovered a right-sided adrenal mass that was suggestive of metastatic disease.

Neuro-ophthalmic examination findings showed that visual acuity was hand movements in each eye. The pupils with surgical iridectomies reacted sluggishly but without an afferent defect. Optokinetic nystagmus was absent. Results of ophthalmoscopy of the retina and optic nerves were normal. A T1-weighted magnetic resonance image (MRI) showed diffuse myelomalacia that was unchanged from a previous MRI of April 2, 1996, done before loss of vision. No contrast enhancement was seen on T1-weighted MRIs that showed only the craniotomy defect. Results of a lumbar puncture done to exclude carcinomatous meningitis were negative, with a white blood cell count of 0 × 10^3/L, a red blood cell count of 4 × 10^6/L, a glucose level of 3.3 mmol/L, and a protein concentration of 0.0022 g/L; and findings of cerebrospinal fluid cytologic examination showed no malignant cells. Serum blood test results included an erythrocyte sedimentation rate of 10 mm/h, an antinuclear antibody titer of 1:80, and a negative rheumatoid factor.

After transfer to the neuro-ophthalmology service, an ERG was ordered and blood was drawn for CAR autoantibodies. Before these results were available, therapy with IV Ig (400 mg/kg per day) was initiated immediately. The next day, visual acuity improved to 20/50 OD and 20/200 OS. By the third day of IV Ig therapy, visual acuity recovered to 20/40 OS and remained stable in the right eye. Despite the improvements in visual acuity, Goldmann visual field perimetry results showed poor responses in the right eye (Figure 1, A) and the left eye (Figure 1, B). Electroretinographic amplitudes at this time were reduced by 40% in the right eye and 50% in the left eye (Figure 1, C). The patient received 2 additional days of IV Ig therapy for a total dose of 2 g/kg over 5 days. Results of Western blot analysis of her serum were positive for retinal 46-Kd autoantibodies (Figure 1, D). Results of reexamination 2 weeks later (May 28, 1996) showed that visual acuity remained 20/50 OD and 20/40 OS. However, there was marked improvement in her visual fields. Goldmann visual field perimetry results now were normal in the left eye (Figure 1, E) and revealed a superior scotoma coming out of the blind spot in the right eye (Figure 1, F). Results of explorative laparotomy revealed metastatic adenocarcinoma. When the patient did not return for further follow-up, inquiries revealed that she had been admitted to a local hospital and had died but that she was not blind.

CASE 2

A 77-year-old woman complained of difficulty driving at night. During the previous 2 to 4 weeks she had begun to lose vision in the right eye, followed by loss of vision in the left eye. She was blind for 1 week before our examination. She had no history of cancer. An MRI showed no abnormalities of the optic nerves or the optic chiasm but showed white matter changes throughout the centrum semiovale. Results of lumbar puncture showed no white blood cells, 2 red blood cells, a protein concentration of 0.0041 g/L, and a glucose level of 2.9 mmol/L. However, no cytologic examination was performed. Results of a left temporal artery biopsy examination showed no evidence of giant cell arteritis. Results of a biopsy examination of the right side showed only a peripheral nerve, but no artery. She was already taking prednisone, 80 mg/d, for the previous 2 weeks for a presumed diagnosis of giant cell arteritis. However, she continued to lose vision rapidly. Medical records showed that at the time she started taking prednisone, vision was 20/60 OD and hand movements in the left eye.

Results of neuro-ophthalmic examination revealed that vision was light perception in both eyes. Pupils showed only a trace reaction to light. Eye movements were full in both eyes. Results of ophthalmoscopy were normal. Optokinetic nystagmus was absent. Results of neurologic examination showed a mild, right peripheral, seventh nerve palsy that was presumed to be caused by a temporal artery biopsy that contained a peripheral nerve. An ERG showed no response in either eye (Figure 2, A). A diagnosis of CAR was made. She was admitted to the hospital and immediately given IV Ig (400 mg/kg), while treatment with prednisone (80 mg/d) was continued. After 5 days of IV Ig treatment, there was no change in light perception vision in both eyes.

A search for an occult malignant neoplasm revealed a normal chest computed tomographic scan, but an abdominal and pelvic computed tomographic scan revealed thickening of the wall of the uterus and para-adrenal adenopathy. Results of cervical biopsy examination revealed...
adenocarcinoma. Explorative laparotomy findings revealed that the cancer had spread beyond the uterus into the peritoneal cavity.

A pretreatment serum sample was positive for a 23-Kd band against recoverin (Figure 2, B). Daily serum sample results after administration of IVIg showed a disappearance of this band, thereby suggesting that the treatment decreased antibody production.

Reexamination of the patient 3 weeks after completion of IVIg treatment showed that vision was still light perception in both eyes. No additional IVIg was administered, and the prednisone administration was rapidly tapered.

CASE 3

A 71-year-old man with adenocarcinoma of the pancreas complained of loss of vision in his right eye that progressively worsened for 2 to 4 weeks. He had no complaints about vision in the left eye. Because of the presence of papilledema, he was referred to the neuro-ophthalmology service.

Results of neuro-ophthalmic examination revealed that visual acuity was 20/400 OD and 20/20 OS. The pupils showed a right afferent defect. Humphrey visual field results showed little response in the right eye (mean, −29.86 dB) (Figure 3, A) and arcuate and nasal defects
in the left eye (Figure 3, B). Results of ophthalmoscopy showed optic disc edema in both eyes.

A contrasted MRI of the brain and optic nerves was normal. Results of lumbar puncture revealed an opening pressure of 180 mm of water. Results of cytologic examination of the cerebrospinal fluid were negative for malignant neoplasms. The cerebrospinal fluid cell count showed no white blood cells and 2 red blood cells. The cerebrospinal fluid protein concentration was 0.0021 g/L and the glucose level was 3.9 mmol/L. He received 3 days of intravenous methylprednisolone acetate (1 g/d) followed by prednisone (1 mg/kg) daily for the remaining 2 weeks.

Results of a follow-up examination 1 month later showed that visual acuity was still 20/400 OD and 20/20 OS. However, there was substantial improvement in the visual field defect of the right eye (mean, −19.51 dB) (Figure 3, C). He declined visual field testing for the left eye. One week later, this improvement in the right eye had reverted to almost pretreatment levels (mean, −27.99 dB) (Figure 3, D). The left eye still had arcuate and nasal scotomas (Figure 3, E). He then received a dose of IV Ig (400 mg/kg). Because of shortness of breath and itching, he declined further treatment.

Results of a follow-up examination 2 days later showed improvement of the visual field defect in the right eye (mean, −19.70 dB) (Figure 3, F), but visual acuity remained unchanged. A month later, the right optic nerve became atrophic, but visual acuity remained stable. He declined visual field testing. A workup for pain in the left hip revealed metastasis in the left femur that was treated by bipolar left hip hemiarthroplasty. A bone scan also showed metastatic disease to both humeri. Palliation radiation therapy to the left hip was initiated, but after 1800 cGy over 6 fractions, he declined further treatment.

His pretreatment serum sample was positive for a 46-Kd band that was against enolase (Figure 3, G).

**COMMENT**

To our knowledge, this is the first report describing the use of IV Ig in the treatment of paraneoplastic visual loss. The results of treatment were mixed. In our first patient...
with CAR, IVIg treatment contributed to a reversal of visual loss. Spontaneous improvements of visual function have not been documented in patients with untreated CAR.3,5,7,11,12,14,15,22,23 Therefore, it is reasonable to assume that improvements in visual function in this patient were treatment related. However, in our second patient with CAR there was no improvement. The rarity of CAR would exclude treatment evaluation in any masked, controlled fashion, thus, we must rely on case reports for insights into the evaluation of new therapies for this disorder.

A review of the medical literature shows improvements of visual function with corticosteroid treatment of paraneoplastic visual loss. Of the 33 patients described in 19 reports and summarized in the Table, 10 (62%) of 16 patients who received corticosteroids recovered visual function. In most of these patients, the degree of visual impairment at treatment initiation was much less severe than that seen in our first 2 patients. In fact, only Klingele and associates3 treated a patient with the same degree of severe visual impairment. They found that recovery of visual function was modest with corticosteroid therapy, improving only from hand movements to counting fingers.4 In contrast, our first patient recovered from hand movements to 20/50 OD and 20/40 OS with IVIg therapy. Keltner and associates5 found recovery from 20/200 to 20/40 and Rizzo and Gittinger11 reported recovery from 20/200 to 20/20 with oral prednisone treatment. Our second patient received similar doses of corticosteroids before administration of IVIg, but she had no response to either therapy. Our third patient with paraneoplastic optic neuritis had improvements of visual field with corticosteroid therapy that relapsed, but then he responded to administration of a single dose of IVIg.

Early treatment successes of CAR-induced visual loss may be evanescent. This is illustrated by corticosteroid-treated patients who experienced transient visual improvements.5,8,9,12,22 In fact, the patient described by Keltner and associates3 whose visual acuity was repeatedly corticosteroid responsive and had improved from 20/200 to 20/40 finally declined to counting fingers in both eyes and was no longer responsive to corticosteroid administration. Because of the severely limited lifespan of our 3 patients with widespread metastatic disease, we do not know if the improvements of visual function achieved with IVIg use were maintained in the long term. However, maintenance of visual function did markedly improve their quality of life.

Although IVIg administration has not previously been described for CAR or paraneoplastic optic neuritis, IVIg has been used in the treatment of other paraneoplastic disorders. Moll and associates,24 in a single case report, found a reversal of neurologic deficits with IVIg treatment of paraneoplastic cerebellar degeneration. The efficacy of IVIg was later challenged in a larger study of paraneoplastic encephalomyelitis and subacute sensory neuropathy.25 Uchuya and associates25 found that IVIg treatment of paraneoplastic encephalomyelitis and subacute neuropathy resulted in some stabilization and slight improvements of neurologic deficits. Although the effect seen by Moll and associates24 was most likely caused by the effects of IVIg therapy, their patient had also received plasmapheresis. Because our first patient received only IVIg, it is likely that such therapy contributed to the recovery of function; perhaps the same is true for the recovery of the patient described by Moll and associates.24

Neuronal degeneration is believed to play a role in the lack of clinical recovery with paraneoplastic disease of the central nervous system. Uchuya and associates25 reported that the beneficial effects of IVIg use were more evident with paraneoplastic disease involving the peripheral nervous system. It is well recognized that the peripheral nervous system has better regenerative capabilities than the central nervous system (including the retina and optic nerve), thus perhaps contributing to the better results of treatment of the peripheral nervous system compartment. For paraneoplastic involvement of the central nervous system, prompt institution of therapy seems to be a major factor in reversal of visual loss and neurologic deficits. In our first patient and that of Moll and associates,24 IVIg therapy was begun early, presumably before irreversible neuronal degeneration. Although IVIg treatment has been reported to reverse the long-term visual loss of optic neuritis caused by demyelination,20 IVIg treatment was not effective in our second patient, presumably because of irreversible neuronal degeneration of retinal photoreceptor cells. For this reason, we began treatment of patient 1 immediately and within a few days of onset of visual loss. Thus, we believe that IVIg treatment was initiated before neuronal degeneration was irreversible. In contrast, IVIg treatment of patient 2, initiated weeks after loss of vision, was probably unsuccessful because of irreversible neuronal degeneration. Treatment may be initiated before completion of the diagnostic workup for CAR, which includes an ERG and serum autoantibody titers. However, metastasis16,17 and radionecrosis18,19 as causes of visual loss must always be excluded, as done in our patients. Reductions in the amplitude of the ERG seen in our patients and the positive autoantibodies, together with the absence of metastasis and radionecrosis of the visual system, confirm that our patients had paraneoplastic visual loss. Although it would have been ideal to obtain a pretreatment ERG of patient 1, we did not want to delay treatment.

The mechanisms involved in clinical recovery with antineoplastic therapy are unclear. This is in large part because of the incomplete elucidation of the mechanisms involved in the pathogenesis of paraneoplastic disorders. Autoantibodies seem to be the hallmark of paraneoplastic disorders. For CAR, antineuronal21 and antirecoverin22,23 antibodies have been identified. However, the clinical syndrome of CAR is also evident in patients who harbor autoantibodies to as yet unidentified retinal antigens.11,32,22,23 Consequently, these patients have negative test results for the CAR antigen against recoverin. Better known are the antineuronal autoantibodies, which have been characterized for paraneoplastic syndromes affecting the nervous system. These include paraneoplastic encephalomyelitis and sensory neuropathy associated with anti-Hu antibodies, paraneoplastic cerebellar degeneration associated with anti-Yo antibodies, and the Lambert-Eaton myasthenic syndrome associated with P/Q-type calcium channel antibodies.24,25,27,31 Uncharacterized antineuronal antibodies also may be associated with paraneoplasia. For example, paraneoplastic visual loss may be caused by unidentified antineuronal antibodies causing a paraneoplastic optic neuropathy11,32-34 rather than the retinopathy of CAR. If autoantibodies cause paraneoplastic visual loss, then one...
might expect a reduction in the levels of circulating antibodies with successful treatment. In fact, decreases in the levels of circulating autoantibodies were found in some patients with CAR who recovered visual function with corticosteroid treatment. Moreover, decreases in autoantibodies were also reported by Moll and associates in their Visual Function in Patients With Cancer-Associated Retinopathy*

<table>
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<tr>
<th>Study</th>
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*F indicates female; M, male; CF, counting fingers; HM, hand movements; LP, light perception; NLP, no light perception; and ellipses, not described.
However, the work of Bain and associates\textsuperscript{31} suggests that reductions in the levels of circulating calcium channel autoantibodies contributed to improved motor strength in a different paraneoplastic disorder, the Lambert-Eaton syndrome. Similarly, in the only patient who had serial serum sample evaluations, we found that the 23-Kd band disappeared the day after the first IVIg treatment, thereby suggesting that IVIg treatment reduced the levels of circulating autoantibodies in CAR, perhaps by neutralizing the autoantibody.

Many hypotheses have been invoked as mechanisms for the therapeutic effects of IVIg in neurologic disorders. Some of these have been summarized in a recent review by Dalakas,\textsuperscript{33} and include (1) immunomodulation of antibody production by B lymphocytes, (2) activation of cytokines such as interleukins or tumor necrosis factor that modulate humoral and cell-mediated immunity, (3) neutralization of pathogenic autoantibodies by anti-idiotypic antibodies, and (4) neutralization of superantigens involved in autoimmunity by neutralizing antibodies among others. Whatever the mechanism, it seems that IVIg may be used successfully as a treatment modality for paraneoplastic visual loss.

Like any medication, IVIg is not without adverse effects. Although 2 patients tolerated IVIg treatment without adverse effects, our third patient did not continue treatment because of itching and shortness of breath. We now premedicate patients with acetaminophen and diphenhydramine hydrochloride before administration of IVIg. Complications of IVIg treatment include deep vein thrombosis, congestive heart and renal failure, headache, rash, leukopenia, neutropenia, proteinuria, pruritus, aseptic meningitis, and dyspnea.\textsuperscript{35,36} With these in mind, the use of IVIg as an alternative agent for treating paraneoplastic visual loss in patients who are clinically unresponsive to corticosteroid treatment, or as an adjunctive therapeutic modality for corticosteroid responders who develop intolerant adverse effects, remains to be further evaluated.

Accepted for publication October 14, 1998.

Supported by grant EY-07982 (Dr Guy) and core grant EY-08571 from the National Eye Institute, National Institutes of Health, Bethesda, Md, and in part by an unrestricted departmental grant from Research to Prevent Blindness Inc, New York, NY.

We thank Berry Jordan, PhD, and Mabel Wilson for technical and editorial assistance in the preparation of the manuscript.

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REFERENCES