Bilateral optic neuropathy with IgGκ multiple myeloma improved after myeloablative chemotherapy

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ABSTRACT

Article abstract A 49-year-old woman with immunoglobulin Gκ multiple myeloma developed progressive visual loss with bilateral upper and lower central arcuate scotomas. Funduscopic and electrophysiologic studies indicated bilateral optic neuropathy. The immunoglobulin G fraction of the patient’s serum reacted with retinal ganglionic cells in bovine retina. The visual abnormalities remitted after myeloablative chemotherapy and disappearance of the paraprotein.
Otic neuropathies constitute a small fraction of patients with paraneoplastic visual disturbance (table), most of whom have retinal injury. Many patients with photoreceptor cell degeneration have serum antibodies that recognize a 23-kd photoreceptor cell protein, termed the cancer-associated retinal (CAR) antigen, or other autoantibodies to retinal antigens. Paraneoplastic optic neuropathy is a rare complication of cancer, most frequently reported in patients with lung cancer. We treated a patient with immunoglobulin (Ig) Gκ multiple myeloma who developed progressive bilateral upper and lower central arcuate scotomas. Repeated funduscopic examinations showed no retinal pathology, and electrophysiologic studies indicated optic neuropathy. The patient's serum showed immunoreactivity with bovine retinal ganglionic cells. After myeloablative chemotherapy, the scotomas resolved and autoantibody was undetectable.

**CASE HISTORY.**

In March 1995, a 53-year-old woman began seeing "holes in the text" when reading, first in the right eye and then in the left. Colors appeared washed out. The discovery of severe anemia led to the diagnosis of IgGκ multiple myeloma. Over several weeks, the scotomata expanded.

On May 31, 1995, her neurologic abnormalities were limited to the visual system. Visual acuity was 20/20 in both eyes. The patient traced bilateral upper and lower arcuate scotomas on paper when asked to draw the abnormalities in her vision. The pupils were equal in size and briskly reactive to light. Extraocular movements were full without nystagmus. Funduscopy revealed questionable temporal pallor.

Two-meter tangent screen testing demonstrated bilateral upper and lower tight arcuate defects with central sparing. A horizontal step was noted in the arcuate scotoma in the right eye. These findings were corroborated by high-resolution computerized visual field testing (figure 1). The small, centrally spared region extended along the nasal horizontal meridian and was nearly enclosed by advanced loss (20 to 30 dB) within about 1.5 deg of the foveal center. The right eye field showed a similar but more advanced pattern.

Computerized contrast sensitivity testing further characterized visual function in the central fields. Contrast sensitivity was measured for grating patterns, with spatial frequencies ranging from 0.5 to 10 cycles/degrees (c/deg) displayed on a 4-deg field using an adjustment technique (VRG system [Vision Research Graphics Inc., Durham, NC]).
NH]). For spatial frequencies less than 2.0 c/deg the contrast sensitivity was markedly reduced compared with the expected range, consistent with severely constricted central fields. Two spatial frequencies (2.0 and 4.0 c/deg) were also tested on the right eye using a method of constant stimuli. The patient’s performance was within the range of expected normal values for this technique. The results indicate a preserved island of normal visual function in the extremely constricted central visual field.

Ganzfeld electroretinogram (ERG) recordings demonstrated normal B-wave amplitudes and latencies under photopic and photopic flicker conditions. After dark adaptation, responses to blue and white flashes were normal, as was the maximal response of the dark-adapted eyes to white flashes. Focal ERGs were also normal. These studies indicated normal retinal function. Visual evoked potentials were delayed bilaterally, consistent with bilateral optic neuropathy.

Serum IgG levels were not elevated, although an IgGκ paraprotein was detectable using immunoelectrophoresis. Serum viscosity was normal. Cryoglobulin, anticardiolipin, and antiphospholipid antibodies were all absent from serum. Vitamin B12 and folate levels were normal. CSF examination demonstrated total protein, 46 mg/dL; IgG, 8.3 mg/dL (IgG/total protein, 18.3%); glucose, 79 mg/dL; and no cells. Cytology was negative. No oligoclonal bands were detected. MRI of the head with and without contrast was unremarkable.

The patient received combination chemotherapy with cyclophosphamide, Adriamycin, etoposide, and dexamethasone. She reported decreasing vision in the preserved central fields. A repeat CSF analysis showed 0 mg/dL IgG. Myelin basic protein was not detected. Bacterial, fungal, and mycobacterial cultures were negative. Cytology was again negative. Plasmapheresis was begun, but after two exchanges the patient reported ongoing shrinkage of the islands of preserved vision. Although repeat MRI of the optic nerves and chiasm demonstrated no abnormalities, 1,000-cGy external beam radiation therapy was delivered to the globes, optic nerves, and chiasm in five 200-cGy fractions. Thiamine, vitamin A, and vitamin B complex vitamins were administered IV. Visual function did not improve.

The patient underwent a series of two courses of myeloablative chemotherapy with subsequent stem cell replacement, and entered hematologic remission with no detectable myeloma paraprotein. The visual scotomas gradually cleared over several months as the upper and lower central arcuate scotomas broke open. Repeat examination in October 1995 demonstrated normal pupillary responses and extraocular movements. Funduscopy demonstrated mild temporal pallor. Color plate performance was perfect, as were 10–2 visual fields.

LABORATORY STUDIES.

The IgG fraction of the patient’s serum and plasmapheresis plasma was prepared using protein A column chromatographic separation, and was biotinylated.5 Immunohistochemical study of bovine retinal sections showed staining of ganglionic cells in a pattern distinct from anti-Hu immunoreactivity (figure 2). Patient, anti-Hu, and control IgG were applied in a concentration of 1.3 μg/mL. Immunoblotting of the patient’s serum IgG fraction (10 μg/mL) using bovine protein homogenates prepared under denaturing conditions was negative. Positive control IgG containing anti-Hu antibodies (also 10 μg/mL) stained a band at the expected molecular weight of 34 kd (not shown). CAR immunoreactivity was not detected (performed by C. Thirkill; not shown). The IgG fraction of patient serum obtained after stem cell transplant did not show immunoreactivity (not shown).
DISCUSSION.

Although rare, paraneoplastic visual disorders can be separated into several distinct syndromes based on clinical and electrophysiologic criteria. Paraneoplastic retinopathies are best documented. In patients with acquired night blindness, funduscopy may demonstrate progressive retinal vitiligo, and ERGs are flat. This syndrome is associated with systemic melanoma. CAR, most frequently associated with small-cell lung cancer, may cause sudden visual loss, night blindness, and photopsias. Funduscopy may reveal retinal vessel attenuation. Photoreceptor degeneration is noted histologically and ERGs are lost. A syndrome of isolated cone dysfunction with achromatopsia has also been described. Bilateral diffuse melanocytic proliferation is a distinctive syndrome in which rapidly progressive visual loss is accompanied by raised deposits in the retinal pigment epithelial layer. The paraneoplastic retinopathies rarely respond to treatment of the associated tumor.

Paraneoplastic optic neuropathies are rare. Retinal ganglionic cell injury may produce findings indistinguishable from optic nerve disease. Our patient demonstrated clinical and electrophysiologic abnormalities indicating optic neuropathy or retinal ganglionic cell injury. Normal electroretinography, including focal ERGs, and bilaterally prolonged visual evoked potentials differentiate this case from photoreceptor cell degeneration. The patient’s serum reacts with ganglionic cells of bovine retina in immunohistochemical studies, but immunoblotting did not identify a specific target antigen. The target antigen may be denatured under the preparative conditions used; alternatively, the antigen may be a glycolipid.

The arcuate scotomas, absence of enhancement on MRI of the optic nerves, negative CSF cytologies, lack of intrathecal production of the IgG paraprotein, absence of other foci of leptomeningeal infiltration, and lack of papilledema all argue against leptomeningeal metastasis. The patient received a low but plasma cell cytoidal dose...
of external beam radiotherapy.

This patient may represent a rare, reversible, potentially immune-mediated paraneoplastic optic neuropathy associated with plasma cell dyscrasias. This rare opportunity to eradicate completely the antineuronal antibody by myeloablative chemotherapy may account for the recovery of visual function.

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REFERENCES


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