Pancreatic Neuroendocrine Paraneoplastic Optic Neuropathy: Confirmation with Antibody to Optic Nerve and Hepatic Metastasis

Thomas L. Slamovits, MD, Jerome B. Posner, MD, Diane L. Reidy, MD, Charles E. Thirkill, PhD, John L. Keltner, MD

Abstract: A 68-year-old woman presented with bilateral visual loss as the only clinical manifestation of an occult pancreatic nonsecretory neuroendocrine tumor (NET). The suspected diagnosis of paraneoplastic optic neuropathy was confirmed using immunofluorescence assays to demonstrate the presence of antibodies in the patient’s serum that reacted with antigen(s) in the optic nerve and in the pancreatic NET hepatic metastasis. Treatment of the underlying cancer was followed by marked improvement in visual function.


Most paraneoplastic neurologic disorders are believed to be immune mediated and often cause symptoms before there is evidence of an underlying malignancy (1,2). Paraneoplastic optic neuropathy (PON) is a rare disorder usually characterized by optic disc edema and vitritis, accompanied by other neurologic manifestations and associated with the collapsing response-mediating protein-5 (CRMP-5) autoantibody, also known as CV2 (3). We report a case of bilateral visual loss due to PON without vitritis and optic disc edema. The patient’s serum contained an antibody that reacted to both optic nerve and the neuroendocrine tumor (NET). Treatment of the NET was followed by marked and sustained recovery of vision.

CASE REPORT

A 68-year-old computer programmer experienced sudden, painless visual loss in both eyes. Over several weeks, her vision deteriorated further and then stabilized. Initially she was able to read but that became increasingly more difficult as did recognizing faces. She denied any systemic or neurologic complaints and took no medications. She was known to be anemic (hemoglobin: 10.6 g/dL), but despite evaluation, the cause of the anemia was not determined.

Two months after the onset of vision loss, visual acuity was 20/100 bilaterally. The patient was unable to recognize any of the Ishihara color plates, and there was a left relative afferent pupillary defect. Eye movements and anterior segment examination were unremarkable, except for mild cataracts. Funduscopy was within normal limits (Fig. 1). Automated visual fields revealed central field loss bilaterally (Fig. 2A). There was no evidence of retinal nerve fiber layer (RNFL) loss in either eye on optical coherence tomography (OCT), and macular OCT also was normal. Neurologic testing disclosed brisk reflexes, unsustained ankle clonus, and possible left Babinski sign.

Initial evaluation was negative for tumor or other occult underlying infectious, inflammatory, or autoimmune abnormalities, including syphilis, sarcoidosis, and systemic lupus erythematosus. Brain and orbital magnetic resonance imaging (MRI) without and with contrast and with fat suppression was normal. Total spine MRI also was unremarkable, as were cerebrospinal fluid studies.

Full-field photopic and scotopic electroretinography was normal, but visual evoked potentials were abnormal in both
eyes. Paraneoplastic markers for CAR and CRMP-5 were negative, as were hematologic studies for Leber hereditary optic neuropathy and neuromyelitis optica. Western blot analysis was negative for anti-retinal antibodies but positive for anti-optic nerve antibodies using an extract of pig optic nerve, showing a reaction at approximately 70 KDa. Western blots and immunochemistry were performed in accordance with previously published protocols (4).

Positron emission tomography showed multiple, low attenuation hepatic lesions, many of which had mildly increased uptake of fluorodeoxyglucose, suspicious for malignancy (standard uptake value range: 2.5–3.8).

FIG. 1. Normal fundus appearance 2 months after the onset of bilateral vision loss.

FIG. 2. Results of automated visual fields and optical coherence tomography at 2 months (A), 10 months (B), and 12 months (C) after the onset of vision loss.
Abdominal MRI identified multiple rim-enhancing hepatic lesions (Fig. 3A), consistent with metastatic disease and a 2.5 × 2.4 cm area of parenchymal prominence in the tail of the pancreas (Fig. 3B). An octreotide scan demonstrated uptake in both the pancreatic and hepatic lesions (Fig. 3C). A liver biopsy confirmed a low-grade, well-differentiated neuroendocrine neoplasm (Fig. 4). Tumor cells were positive for synaptophysin, chromogranin, and CD56 while negative for Hepar, CD34, and MCEA. The MIB-1 (KI-67) proliferation rate was approximately 2%, and reticulin stain was negative. These findings supported the diagnosis of a nonfunctional (non–hormone secreting) pancreatic NET, metastatic to the liver. Tissue from the hepatic metastasis reacted with the patient’s serum and with rabbit anti-optic nerve antisera; no immunoreactivity was found when normal liver tissue was exposed to the patient’s serum and to rabbit anti-optic nerve antisera (Fig. 5).

After right hepatic transarterial embolization, the patient was treated with intravenous immunoglobulin (IVIg) and subsequently with octreotide. Within weeks of starting the therapy, visual acuity gradually improved to 20/30 in each eye. Visual fields also improved (Fig. 2C), while OCT showed bitemporal RNFL loss (Figs. 2B & 2C). The patient was again able to drive and to use her computer.

**DISCUSSION**

While our understanding of paraneoplastic syndromes continues to evolve (2,5), Graus et al (6) proposed the following definition: “a non-classical syndrome with onconeural antibodies (well-characterized or not) and cancer that develops within 5 years of diagnosis of the neurological disorder.” Isolated PON is rare and usually occurs as a manifestation of a more widespread paraneoplastic syndrome, including cerebellar degeneration, cognitive changes, sensory neuropathy, and myelopathy (mimicking neuromyelitis optica). PON presents as acute or subacute, progressive, frequently bilateral, painless loss of vision, and examination may reveal optic disc edema, inflammatory cells in the vitreous, and various visual field abnormalities including arcuate, altitudinal, or paracentral defects (7–10). Pathologic findings of PON include lymphocytic infiltrations, usually with T cells, patchy loss of axons and myelin, and absence of tumor cells (3,11,12).
Most reported cases of PON have a serum antibody to a 62 KDa neuronal antigen termed CV2 and subsequently renamed CRMP-5 (13). Yu et al (14) described this paraneoplastic immunoglobulin G (IgG) autoantibody, a neuronal cytoplasmic protein, a previously unknown 62 Kd member of the CRMP family. Since 1993, they have detected this antibody in 121 cases of paraneoplastic syndromes (14). Cross et al (3) described CRMP-5 IgG optic neuritis, and vitritis, associated with other neurologic abnormalities including altered mental status, cranial neuropathies, movement disorders, myelopathy, and peripheral neuropathy, and cerebellar and autonomic dysfunction. Margolin et al (15) described CRMP-5–positive PON and vitritis as the only clinical manifestation in a patient with small cell lung cancer. Lambrecht et al (16) reported a patient with a glucagon-secreting NET and vision loss presumed to be the result of bilateral optic neuropathy. However, electrodiagnostic and immunologic studies to rule out paraneoplastic retinopathy were not performed and the patient’s evaluation, in contrast to ours, revealed secretion of endocrine markers.

Our patient had several of the typical features of PON, including rapid onset visual loss, but the immunological findings in our patient are unique. Her serum anti-optic nerve antibodies (about 70 KDa on the Western blot) have not been reported previously in a paraneoplastic syndrome (5). Furthermore, these antibodies reacted both with her NET and optic nerve. We are not aware of any previous case of PON in which a disease producing antigen was looked for and found in the neoplasm.

In patients with PON, treatment of the malignancy or immunosuppression usually fails to improve the optic neuropathy, although visual recovery, at times dramatic, as in our patient, has on occasion, been reported (1,11,12,17–19).

The decision to choose embolization in treating our patient’s NET was based on the dual blood supply of the liver. Tumors within the liver receive the majority of their blood supply via the hepatic artery, whereas the hepatic parenchyma receives about three quarters of its blood supply through the portal vein. Inducing vascular occlusion of the hepatic arterial supply can result in selective ischemia and necrosis of the tumor with relative preservation of normal liver. This was followed by administration of IVIg and administration of octreotide. Two years after this therapeutic regimen, our patient retains normal vision.
REFERENCES