



## CRMP-5 Positive Paraneoplastic Optic Neuropathy as Initial Presentation of Small Cell Lung Cancer

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### Abstract

Paraneoplastic neurologic syndromes are manifestations of systemic malignancies. It is recognized as an immune mediated response that can rarely present as an optic neuropathy. Advancement in anti-neuronal antibody testing had led to increased identification of this paraneoplastic process.

We describe a unique case of a 72-year-old male who presented with bilateral blurry vision and was found to have asymmetric optic disc edema on exam. His visual symptoms and exam findings were rigorously investigated with imaging, serology testing, lumbar puncture, ophthalmic ancillary testing, and biopsy. His chest and abdominal imaging were concerning for lung cancer. The suspicion of a metastatic neuroendocrine lung primary was confirmed by fine-needle aspiration biopsy. His serology and cerebrospinal fluid were positive for an anti-neuronal autoantibody known as Collapsin Response-Mediator Protein-5 (CRMP 5). He was subsequently diagnosed with Paraneoplastic Optic Neuropathy (PON) due to metastatic small cell lung carcinoma. Unlike other cases of PON, our patient's vision loss prompted work-up for malignancy. Moreover, he did not demonstrate the typical findings associated with PON such as vitreous inflammation, brainstem dysfunction, or cerebellar dysfunction. With chemotherapy and corticosteroids, his vision recovered. This case demonstrates the importance of recognizing vision loss as a sign of PON, a rare manifestation of systemic malignancy.

### Introduction

Paraneoplastic syndromes occur in less than 10% of cancer patients, and affect the visual system in less than 0.01% of patients. Of the ocular tissues involved, the retina is the most common, presenting as melanoma-associated retinopathy, cancer-associated retinopathy, or paraneoplastic vitelliform maculopathy. Neurologic paraneoplastic syndromes rarely manifest as optic nerve disease known as paraneoplastic optic neuropathy (PON) [1,2].

The most common etiology of PON is a pulmonary microcytic tumor of neuroectodermal origin. This neoplasia develops from enterochromaffin cells of neuroectodermal origin and express antigens with cross-reactivity to the nervous system. With the advent of paraneoplastic serology testing and discovery of new autoimmune proteins, PON is becoming an increasingly recognized autoimmune ocular manifestation of systemic neoplasia. Specifically, Collapsin Response-Mediator Protein-5 (CRMP-5) has been implicated in PON, but the exact pathogenesis to immunogenicity is not known [3].

PON typically presents as a subacute painless and progressive bilateral vision loss typically associated with disc edema and cells in the posterior vitreous. Non-specific visual symptoms may precede systemic manifestations of the primary cancer and may prompt cancer work-up, leading to earlier detection of malignancy.

### Case Presentation

A 72-year-old Caucasian male presented to the emergency department reporting two months of progressively worsening, painless, blurry vision in both eyes. He denied pertinent medical or ocular history. On review of systems, he reported fatigue and unintentional weight loss over the last six months, severe upper respiratory tract infection five months prior. Social history revealed approximately 100 pack year smoking history; and he continues to smoke.

Baseline exam on presentation was significant for best corrected visual acuity of 20/20 OD and 20/25 OS. Mild, longstanding anisocoria was noted without relative afferent pupillary defect. Ishihara color plates were 13/13 in the right eye and 5/13 in the left eye. Dilated ophthalmoscopic

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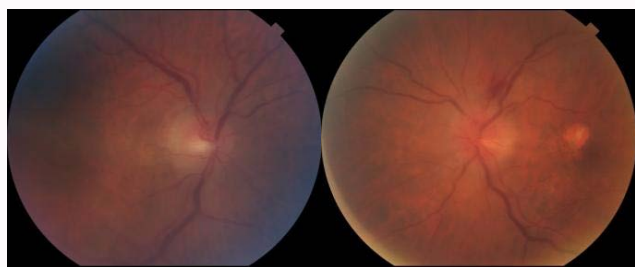
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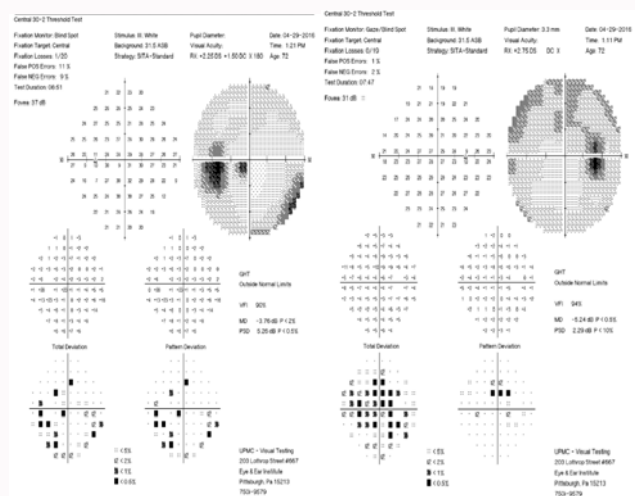
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**Figure 1:** Fundus photos of the optic nerve. The right optic nerve (left image) demonstrates only mild blurring of disc margins. The left optic nerve (right image) has diffuse edema with blurring of disc margins, hyperemia, obscuration of disk vessels, and peripapillary flame hemorrhage.

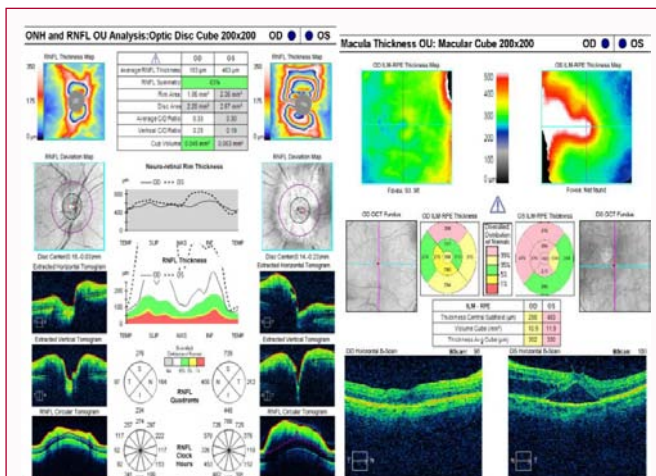


**Figure 2:** Baseline Humphrey Visual Fields (HVF) 30-2 was performed and showed bilateral blind spot enlargement with left cecocentral scotoma.

exam was significant for diffuse disc edema with blurring of disc margins, hyperemia, obscuration of vessels, and a peripapillary flame hemorrhage in the left eye. There is mild blurring of disc margins of the right eye. Baseline Optical Coherence Tomography (OCT) was performed and showed bilateral supranormal Retinal Nerve Fiber Layer (RNFL) with nasal macular edema. Baseline Humphrey Visual Fields (HVF) 30-2 was performed and showed bilateral blind spot enlargement with left cecocentral scotoma. Baseline fundus photos, OCT, and visual field testing are shown in Figures 1-3.

Extensive vascular, infectious, inflammatory, toxic, and metabolic work-up performed and was grossly unrevealing. Lumbar puncture was performed with opening pressure of 22 mmHg. Cerebral spinal fluid (CSF) was positive for elevated IgG (19.7), IgG index (1.12), and IgG synthesis rate (54.6). There was no evidence of infection of malignant cells. Neuromyelitis optica titers were negative. Serum IgG levels were normal, but protein electrophoresis revealed elevated alpha 2 and gamma globulin. Paraneoplastic work-up was positive for collapsin response-mediator protein-5 (CRMP-5) IgG (1:122880)/CV2 autoantibodies from serum and CSF.

A chest X-ray uncovered a focal left hilar opacity and subsequent Computed Tomography (CT) scan revealed multiple lung and liver nodules suspicious for metastatic lung cancer (Figures 4-6). Magnetic Resonance Imaging (MRI) of the brain and orbits was performed and there was no abnormal signal enhancement in the optic nerves/chiasm or evidence of intracranial or orbital metastatic disease (Figure 7).



**Figure 3:** Baseline optical coherence tomography was performed and showed bilateral supranormal retinal nerve fiber layer (left image) and nasal macular edema (right image).

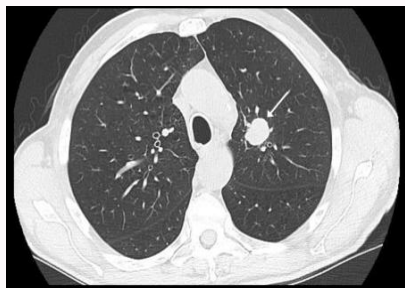


**Figure 4:** Initial portable chest X-ray showing left focal hilar opacity.

Magnetic resonance angiogram and venogram were normal without evidence of sinus thrombosis. A Positron Emission Tomography (PET) scan ruled out other sites of metastasis. Fine needle aspiration of his liver with synaptophysin immunostain indicates a neuroendocrine tumor. The same sample was also weakly TTF-1 positive, indicating a likely lung primary (Figure 8). All-together, his findings were consistent with the diagnosis of small cell lung cancer.

The patient did not adhere to treatment recommendations. One month after initial presentation, he returned with worsening of vision. On exam, his best corrected visual acuity had decreased to 20/40 - in the right eye and 20/200 within the left eye, with a left afferent pupillary defect. Ophthalmologic exam and OCT showed worsening disc edema. His visual field showed worsening internal enlargement of blind spots. Given his visual function deterioration, he was treated with high dose steroids (Intravenous (IV) methylprednisolone 1 gram for 5 days) and oral acetazolamide 500 mg three times per day. The patient was again referred to oncology and ultimately received 3 cycles of carboplatin/bleomycin/etoposide chemotherapy regimen.

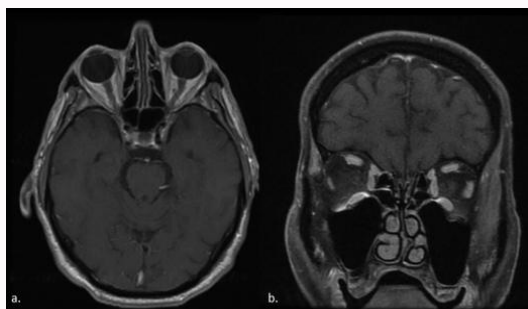
At the time of his last follow-up visit, his best corrected visual acuity had improved from legal blindness to 20/30 in the right eye and 20/20 in the left eye. Color perception tested by Ishihara plates improved bilaterally. Final visual field testing showed improvement



**Figure 5:** Chest computed tomography scan revealed left upper lung nodule (arrow).



**Figure 6:** Abdominal computed tomography scan revealed three lytic hypodense lesions compatible with metastatic lung cancer.

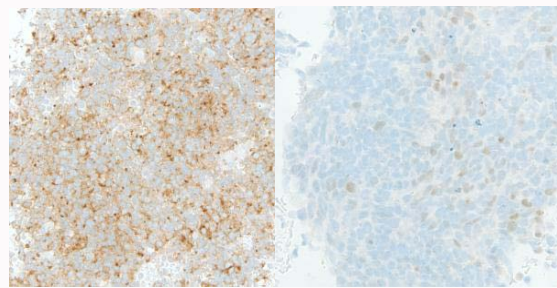


**Figure 7:** Normal magnetic resonance imaging of the brain and orbits.

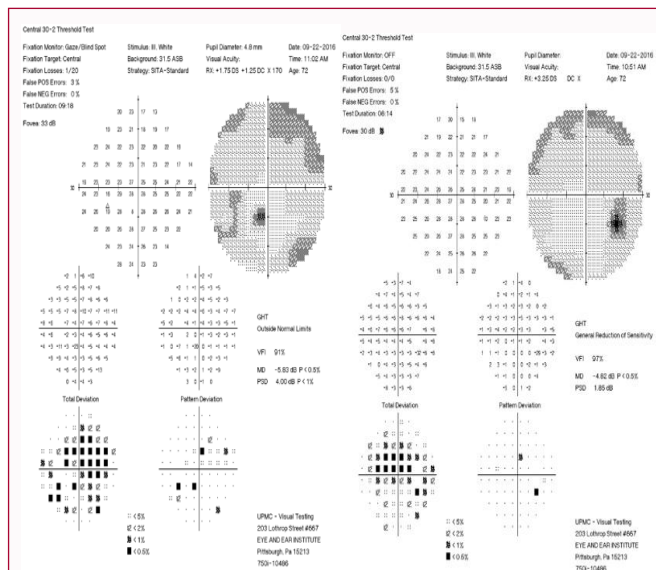
of bilateral blind spot enlargement and cecocentral scotoma. OCT showed significant improvement of RNFL edema bilaterally.

## Discussion

Paraneoplastic syndromes rarely affect the visual system, particularly the optic nerve. Despite its rarity, it was first described by Davies in 1961 as carcinomatous neuropathy with disc edema in a patient with small cell lung cancer (SCLC) [4]. Similarly, in 1982, Kornguth reports a visual paraneoplastic syndrome associated with binocular vision loss in the setting of SCLC [5]. These patients were found to have high titers of circulating antibodies that immunologically cross-react with ocular tissue. These same immunoglobulins were also isolated in the Cerebrospinal Fluid (CSF), indicating a compromised blood-brain barrier [5,6]. Histopathologic evidence reveals extensive loss of ganglion cells that coincide with high levels of serum autoantibodies [7,8]. An extensive array of paraneoplastic blood tests are available from several labs including autoantibodies against neurons, glial cells, oligodendrocytes, muscle cells, and plasma membrane channels. Our patient's CSF and serum was positive for CRMP-5 autoantibodies. CRMP-5 is a 62-kd neuronal cytoplasmic protein found in central and peripheral neurons, retina and optic



**Figure 8:** Positive synaptophysin immunostain for neuroendocrine tumors (left image). Weakly positive TTF1-nuclear stain (right image).



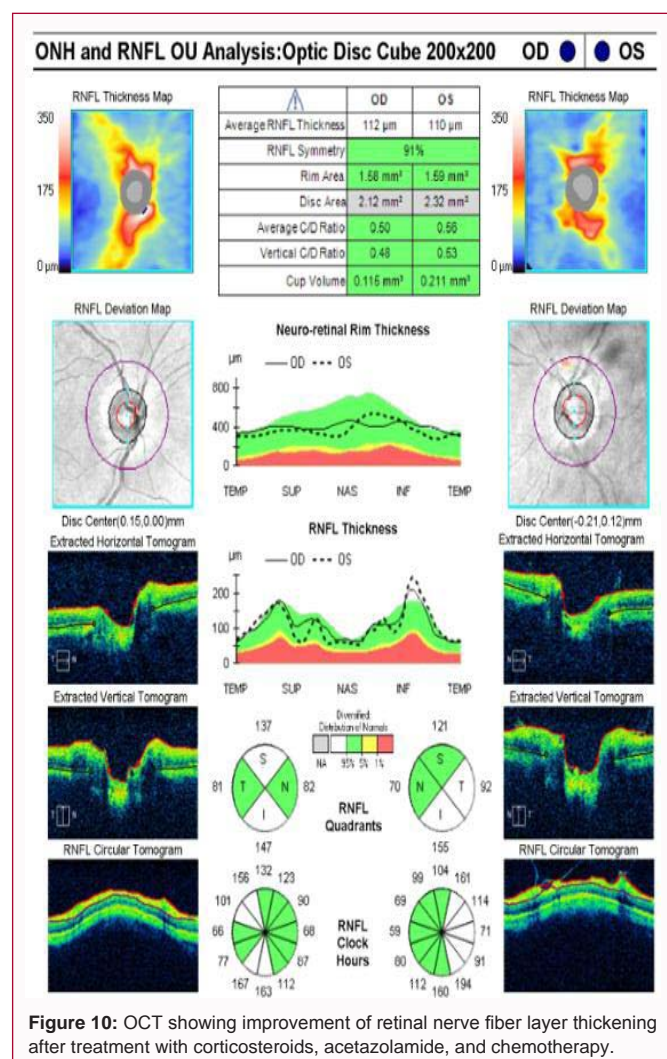
**Figure 9:** HVF documents improvement of bilateral blind spot enlargement and left cecocentral scotoma after treatment with corticosteroids, acetazolamide, and chemotherapy.

nerve [9]. Optic neuropathy has been reported to occur in only 1 of 12 patients with paraneoplastic syndrome defined by anti-CRMP-5/CV2 antibodies [10]. Lung cancer was the related malignancy in 77% of patients with anti-CRMP antibodies paraneoplastic optic neuropathy and retinopathy [7]. Other malignancies causing optic neuropathy include bronchial, nasopharyngeal, neuroblastoma, and lymphoma [9].

The most common presenting symptoms of PON are non-specific visual complaints (blurry vision, flashes of light, and tunnel vision), neurological sequela and vitritis [1,2,6]. Neurologic sequela include internuclear ophthalmoplegia, mononeuropathy, parkinsonism, myoclonus, akathisia, ataxia, dysphagia, and unexplained neurologic deterioration [2]. Our case is unique because our patient did not have any neurological deficits or cells in the vitreous.

If a primary neoplasm is known in the setting of optic neuropathy, the differential diagnosis should include carcinomatous meningitis, orbital or intracranial metastasis, direct infiltration of the optic nerves, toxicity to chemotherapy, or paraneoplastic optic neuropathy. Work-up should include MRI with and without contrast to exclude metastatic compressive or infiltrative lesion. Lumbar puncture with opening pressure, paraneoplastic panel, cytology, and flow cytometry will assess for malignant cells in the CSF [11]. Magnetic resonance venography should be considered to rule out sinus thrombosis that





may lead to elevated intracranial pressure and vision loss. In the setting of disc edema and negative work-up above, paraneoplastic optic neuropathy should be strongly considered. Diagnostic paraneoplastic panel should be performed to confirm the diagnosis.

The goal of treatment is to reduce the systemic titers of autoantibodies damaging the nervous system. Given that the prevalence of paraneoplastic syndrome is very low, no large scale randomized trial has been performed. The primary treatment should address the underlying cancer, and may be achieved with surgery, chemotherapy, hormone therapy, and/or radiation. Treatment of the underlying neoplasm has been shown to significantly improve vision [11]. Other treatments may include immunotherapies such as steroids, Intravenous Immune Globulins (IVIG), and plasma exchange. It has been shown that treatment with corticosteroids alone can improve symptoms in patients with paraneoplastic optic neuropathy. The most studied treatment modality is high dose IV steroids, which can significantly improve vision and disc edema [12,13]. One study has also demonstrated the effectiveness of targeted immunosuppression such as intravitreal triamcinolone in patients who experienced progressive vision loss despite chemotherapy [14]. Our patient was treated with high dose corticosteroids (IV methylprednisolone), oral acetazolamide, and chemotherapy with significant improvement of vision and disc edema.

Ophthalmologic signs or symptoms may be the first manifestations of cancer. Diagnosis of paraneoplastic optic neuropathy with positive serological testing helps hasten the diagnosis of malignancy. Early diagnosis and treatment can help prevent permanent vision loss and greatly improve quality of life.

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