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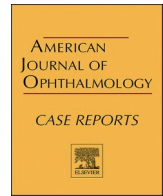
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# Bilateral vision loss as the initial presentation for central nervous system involvement of mantle cell lymphoma: A case series

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## ABSTRACT

**Purpose:** Mantle cell lymphoma is a rare aggressive subtype of non-Hodgkins B cell lymphoma. It typically presents with asymptomatic monoclonal lymphocytosis, lymphadenopathy or bulky extranodal disease. Mantle cell lymphoma rarely affects the central nervous system. We present two cases in which vision loss was the initial symptom of central nervous system involvement by the malignancy.

**Observations:** Both patients initially received high dose intravenous steroids with notable improvement in their vision.

**Conclusions and importance:** Early detection and management of optic nerve infiltration by mantle cell lymphoma is essential as it improves visual outcomes and enables prompt management of the patient's systemic disease.

## 1. Introduction

Mantle cell lymphoma is a rare, aggressive subtype of non-Hodgkins B cell lymphoma representing 5–10% of all non-Hodgkins lymphoma.<sup>1</sup> Patients can present with asymptomatic lymphocytosis, bulky extranodal disease (splenomegaly, lymphomatous polyposis in the gastrointestinal tract, kidney masses), or generalized lymphadenopathy.<sup>2</sup> Central nervous system (CNS) involvement in this condition is uncommon and present in 4–26% of cases. However once the CNS is involved, the disease has an extremely poor prognosis with a median survival of approximately 5 months.<sup>1,3</sup> Up to one quarter of individuals with nervous system involvement will have concomitant ophthalmic disease.<sup>4</sup> Mantle cell lymphoma involving the ocular adnexa occurs in 1–4% of people and is more common in patients with disseminated disease.<sup>5,6</sup> Intraocular involvement has only been reported in 10 prior cases and has a propensity for uveal tissue presumably due to its rich vascular supply.<sup>3,4,7</sup> Even less common is infiltration of the optic nerve, with only 3 prior reported cases in the literature.<sup>3,7,8</sup> We present two cases of optic nerve infiltration with mantle cell lymphoma as the first sign of central nervous system involvement of the malignancy.

## 2. Case report

### 2.1. Patient 1

An 84 year-old man presented with a six month history of bilateral painless progressive visual decline. He endorsed poor energy, fatigue and loss of appetite over one month. He denied jaw claudication, scalp tenderness, myalgias, headaches and transient vision loss. He had a complex past medical history with a diagnosis of mantle cell lymphoma eight years prior treated with rituximab and bendamustine resulting in complete remission. The patient remained on maintenance rituximab every three months. He had a recurrence of his cancer two years prior to presentation with remission on subsequent cycles of rituximab.

On examination, the patient was frail and cachectic. His vision was hand motion in the right eye and count fingers at 1 foot in the left eye. He had a right relative afferent pupillary defect. Extraocular motility was normal. Slit lamp examination showed an unremarkable anterior segment. Fundoscopy revealed bilateral optic nerve swelling with a peripapillary hemorrhage inferior to the left optic nerve. The patient also had large soft drusen bilaterally in keeping with macular degeneration (Fig. 1). General neurologic examination was normal. His physical exam was notable for a large, matted, nontender right preauricular lymph node.

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Magnetic Resonance Imaging (MRI) with and without contrast demonstrated bilateral thickening of the pre-chiasmatic optic nerves with associated diffuse enhancement and diffusion restriction of the optic nerves in keeping with lymphomatous infiltration (Fig. 2). 18F-Fluorodeoxyglucose Positron Emission Tomography scan revealed numerous areas of hypermetabolic foci in the head, neck, thorax, renal parenchyma, and lymph nodes. Non-contrast Computed Tomography imaging of the chest abdomen and pelvis corroborated this with numerous areas of lymphadenopathy as well as nodular renal and biliary involvement. Cerebrospinal fluid analysis revealed 255 white blood cells (77% cells being atypical lymphocytes), elevated protein at 134, and normal glucose. Flow cytometry confirmed a monoclonal lymphomatous population within the cerebrospinal fluid (CD5 kappa B cell population) in keeping with mantle cell lymphoma. Treatment with intravenous steroids, intrathecal methotrexate, ibrutinib and rituximab was initiated with improvement in the patient's vision. Unfortunately, four months following this presentation, the patient ultimately succumbed to his systemic illness.

## 2.2. Patient 2

A 65 year-old man was seen with a three week history of progressively worsening blurry vision. The patient had a complex medical history of Stage IVB pleomorphic mantle cell lymphoma (TP53+) in the colon and rectum with good response to acarlubrutinib. Nine months after his initial diagnosis of mantle cell lymphoma, the patient presented with left eyelid swelling and ptosis. His 18F-Fluorodeoxyglucose Positron Emission Tomography scan demonstrated hypermetabolic tissue in the left lacrimal gland and base of the tongue. He underwent radiation therapy to the base of tongue and lacrimal gland with good response.

Twelve months following initial diagnosis, his vision began to worsen and images appeared dark. He endorsed a persistent, severe frontal headache but no other neurologic symptoms. On exam, his vision was count fingers at 4 feet in the right eye and 20/400 in the left eye. Extraocular motility was normal. He had mild periorbital edema of the left upper eyelid. Fundoscopy demonstrated right optic nerve swelling with hyperemia. The left optic nerve appeared normal (Fig. 3). Magnetic resonance imaging with contrast showed diffuse enlargement and enhancement of both optic nerves with associated diffusion restriction in keeping with a hypercellular infiltrative optic neuropathy (Fig. 4). Cerebrospinal fluid analysis demonstrated an elevated white blood cell count (25) with 25% abnormal cells in keeping with lymphoma. Flow cytometry demonstrated CD-5 positive, kappa-restricted B cells in keeping with mantle cell lymphoma.

During his hospital course, he was started on intravenous methylprednisolone and transitioned to an oral prednisone taper on discharge with rapid improvement of his visual acuity. Two months following

discharge his optic nerve swelling had resolved and he had 20/20 vision bilaterally with no dyschromatopsia or visual field defect. For his disseminated central nervous system disease he underwent further radiation, chemotherapy and ultimately Chimeric Antigen Receptor T cell (CAR-T cell) therapy.

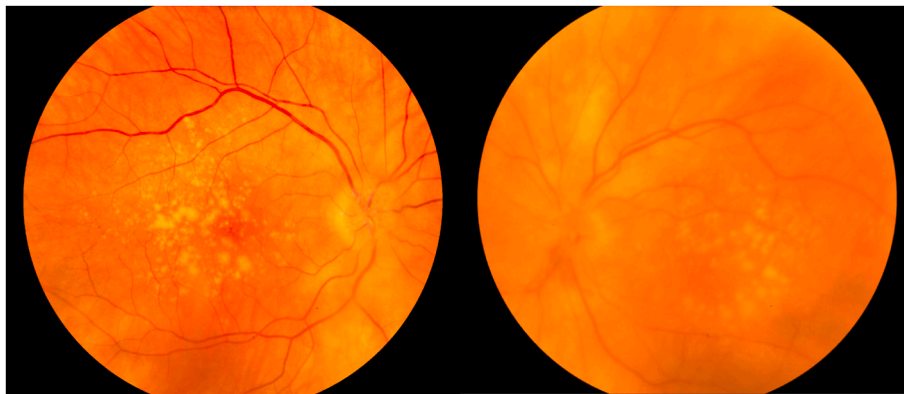
## 3. Discussion

Mantle cell lymphoma is a rare form of non-Hodgkins B cell lymphoma with a significant male predominance in patients over 60 years of age. Patients are often diagnosed when the cancer is at advanced stages with multiple lymphadenopathies or extra-nodal involvement. Ophthalmic manifestations of mantle cell lymphoma are typically orbital in nature as it can affect the lacrimal glands, periorbital and adnexal structures. Central nervous system involvement is not common and portends a poor prognosis.<sup>9</sup> Risk factors for central nervous system involvement include blastic morphology, high MIB-1/Ki-67 immunostaining, high serum lactic acid dehydrogenase levels, and a high-risk International Prognostic Index score.<sup>1</sup>

Optic nerve infiltration by mantle cell lymphoma can present with a normal appearing fundus or with optic nerve swelling with or without cotton wool spots and/or peripapillary hemorrhages. Magnetic resonance imaging demonstrates enlargement and enhancement of the optic nerves, with supporting cerebrospinal fluid analysis revealing the presence of malignant cells as evidence of leptomeningeal spread.

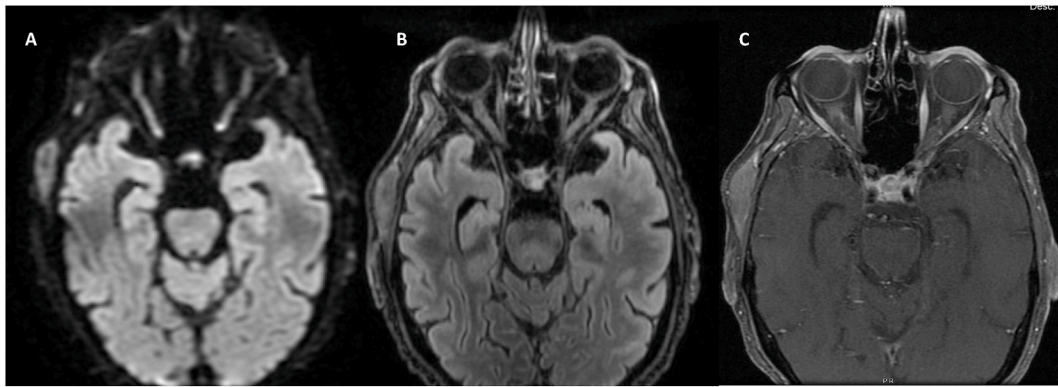
There is currently no standard treatment for optic nerve infiltration. Prior cases reported treatment with central nervous system penetrating chemotherapy, intravitreal methotrexate and whole brain radiotherapy.<sup>3,8</sup> Our patients demonstrated a significant response to high dose intravenous steroids, resulting in an improvement in one patient back to normal visual acuity without dyschromatopsia or a visual field defect. Both patients received further treatment for their leptomeningeal mantle cell lymphoma in addition to the solumedrol, however, the steroids provided the most significant benefit with respect to improvement of visual function.

Vision loss in patients with a history of mantle cell lymphoma should be evaluated in the context of their systemic malignancy. Although exceptionally rare, providers should have a high suspicion of optic nerve infiltration in patients that have a history of mantle cell lymphoma as this can result in progressive and irreversible vision loss if not addressed in a timely manner. Optic nerve involvement may be the first sign of central nervous system infiltration of mantle cell lymphoma. Early detection and identification of central nervous system infiltration by ophthalmologists enables appropriate treatment and management of the cancer thereby improving overall morbidity and mortality from the systemic illness.



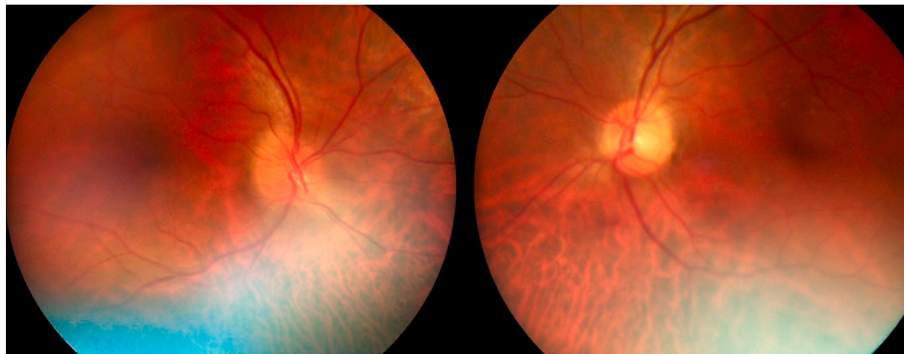
**Fig. 1. Fundus Examination.**

Fundoscopy revealed bilateral optic nerve swelling with a peripapillary hemorrhage inferior to the left optic nerve. Soft drusen was present in the posterior pole in keeping with the patient's history of macular degeneration.



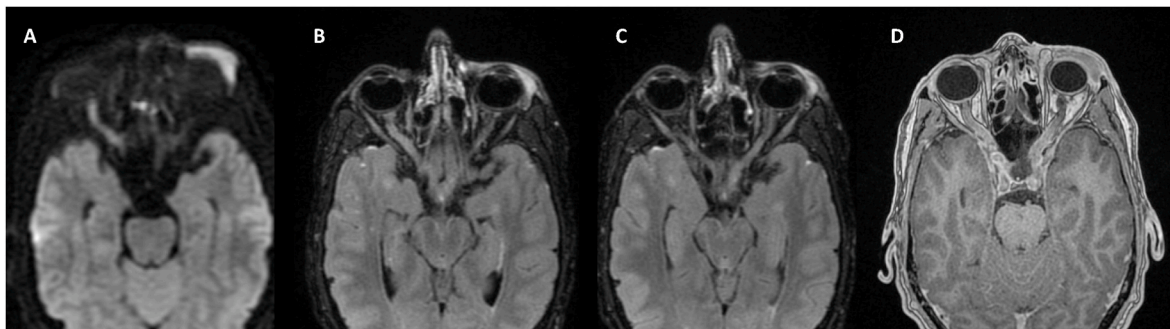
**Fig. 2. Magnetic Resonance Imaging.**

MRI imaging demonstrated markedly thickened optic nerves bilaterally consistent with infiltrative optic neuropathy. The Diffusion Weighted Imaging (DWI) demonstrated diffusion restriction of both optic nerves in keeping with an infiltrative hypercellular optic neuropathy (A). FLAIR images demonstrated enlargement and T2 hyperintensity of the optic nerves bilaterally (B). T1 Contrast enhanced imaging further demonstrated enlargement and mild perineural enhancement of the optic nerves bilaterally (C). Note is made of the right temporal scalp lesion with reduced diffusion also suspicious as a focus of mantle cell lymphoma.



**Fig. 3. Bedside Fundus Examination.**

The images were obtained using a hand-held fundus camera at the bedside. The right optic nerve demonstrated hyperemia and swelling. The left optic nerve appeared normal. There were no abnormalities of the vasculature or posterior pole.



**Fig. 4. Magnetic Resonance Imaging.**

MRI imaging demonstrated markedly enlarged optic nerves with associated reduced diffusion and enhancement. DWI imaging (A) demonstrated marked diffusion restriction of the right optic nerve. FLAIR imaging of the right (B) and left (C) optic nerves demonstrates significant enlargement and mild T2 hyperintensity of the optic nerves bilaterally. Contrast enhanced T1 imaging (D) represents the enhancement of the optic nerves bilaterally. Note is made of the enlarged and enhancing left lacrimal gland with reduced diffusion.

#### Patient consent

Consent to publish this case report has been obtained from the patient #2 in writing. Patient #1 is deceased and therefore written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

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#### Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

### Declaration of competing interest

The following authors have no financial disclosures: LS, CM, SR, MS, NR.

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