INTRAVITREAL METHOTREXATE FOR MANTLE CELL LYMPHOMA INFILTRATION OF THE OPTIC NERVES: A CASE REPORT

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Purpose: To report the successful treatment of a 78-year-old woman with bilateral mantle cell lymphoma involving the optic nerves. Chemotherapy initially was administered in the form of intravitreal methotrexate (MTX) monotherapy and was subsequently combined with systemic ibrutinib.

Methods: Retrospective case report. The diagnosis of CD5-negative mantle cell lymphoma was confirmed via immunohistopathological analysis of an axillary lymph node. Serial ophthalmologic examinations in conjunction with fluorescein angiography, fundus photography, and spectral domain optical coherence tomography were used to assess the treatment response.

Results: Prompt improvement in optic nerve infiltration, no significant side effects, and excellent tolerability were noted after two weekly injections of unilateral intravitreal MTX monotherapy. Combined systemic treatment with ibrutinib and bilateral weekly MTX intravitreal injections then resulted in continued regression of optic nerve infiltration bilaterally as confirmed by serial fundus photography and optical coherence tomography. After eight additional bilateral weekly injections, a mild MTX-associated keratopathy developed, which resolved promptly with cessation of injections and administration of topical lubrication. Six weeks after MTX cessation, but with continued ibrutinib treatment, the optic nerves revealed near-complete resolution of the lymphomatous infiltration and the visual acuity improved.

Conclusion: Intravitreal MTX injections and systemic ibrutinib may represent effective treatment options for patients diagnosed with intraocular mantle cell lymphoma.

RETINAL CASES & BRIEF REPORTS 0:1–5, 2016

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Intraocular mantle cell lymphoma (MCL) is a rare clinical entity. Mantle cell lymphoma is an aggressive and incurable form of non-Hodgkin lymphoma. A B-cell lymphoma subtype, MCL accounts for 6% to 8% of all non-Hodgkin lymphomas with an annual incidence of 0.4 per 100,000 persons in the United States and Europe.[1] The condition most often affects men older than 60 years and generally presents as late stage disease.[2] Mantle cell lymphoma has conventionally carried a poor survival prognosis, and patients have a median overall survival of 3 to 5 years.[1,2]

Herein, we present a case of a patient with bilateral MCL optic nerve infiltration who underwent combination treatment with serial bilateral intravitreal methotrexate (MTX) injections and systemic ibrutinib. To our knowledge, this is the first case report of this unique manifestation of MCL.

Supported by The Clive Hamilton Sell Vision Foundation.

None of the authors have any conflicting interests to disclose.

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Case Report

A 78-year-old woman was admitted to the hospital for progressive vision loss in the right eye over the preceding 2 to

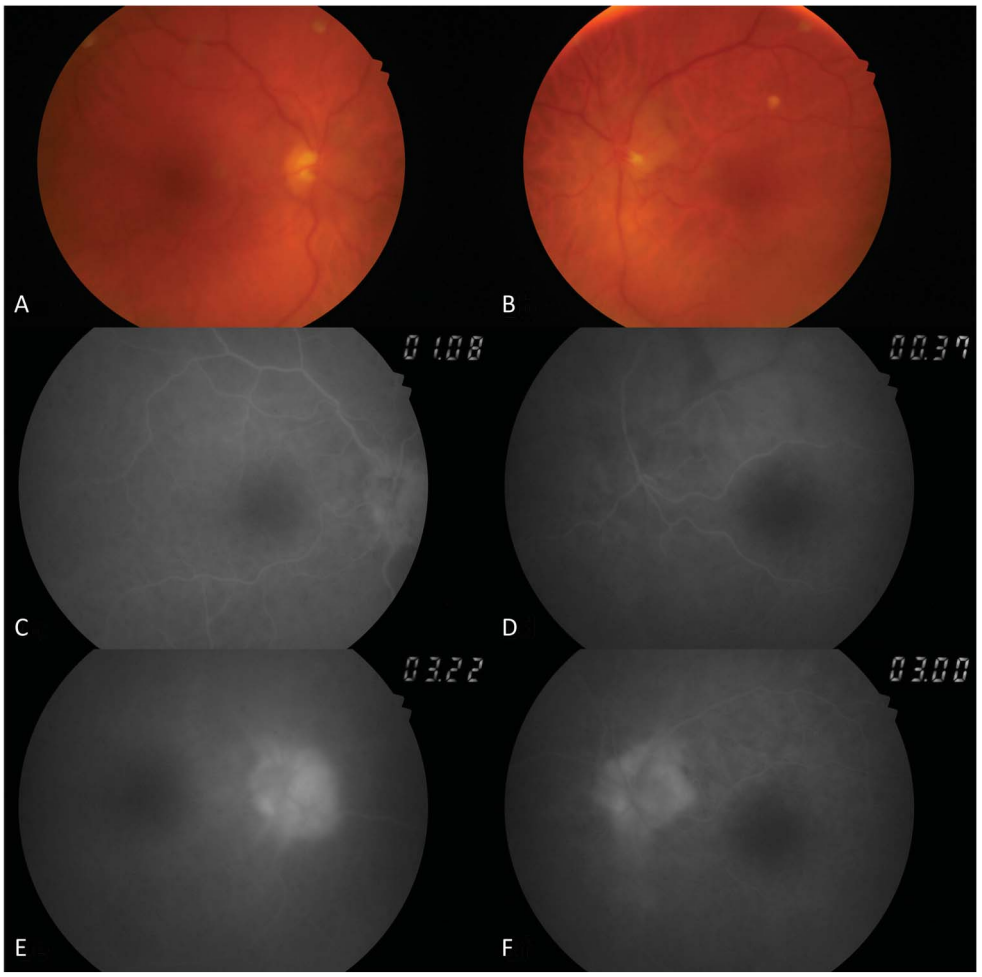

Fig. 1. Fundus photographs (**A** and **B**) demonstrate obscuration of the nasal 180° of the optic disk in the right eye with lymphomatous infiltration and near-complete engulfment of the disk in the left eye. Fluorescein angiography images (**C**–**F**) revealed normal retinal and choroidal circulation with late staining of the optic nerves in both eyes in the areas of lymphomatous infiltration.

3 months and in the left eye over 4 months, which was described as generalized blurring. She reported several ophthalmologic examinations over the preceding 3 months. These examinations were notable for atypical bilateral optic disk edema, but none provided a conclusive diagnosis or management plan. The patient had a history of chronic lymphocytic leukemia with no previous treatment, hypertension, and coronary artery disease with stenting and pacemaker placement. Her medications included lisinopril, carvedilol, and aspirin. She denied history of ophthalmic disease, family history of heritable eye disease, or history of tobacco use.

At the time of our inpatient consultation, her near-uncorrected Rosenbaum visual acuity was 20/20 in the right eye, and counting fingers at 3 feet in the left eye. A mild relative afferent pupillary defect was observed in the left eye. Her confrontational visual fields were grossly full in both eyes. Bedside anterior segment examination revealed normal findings except for 2+ nuclear sclerosis in both eyes. Dilated posterior segment examination revealed grossly clear vitreous without appreciable haze or cells. The macular region was unremarkable except for rare drusen and mild retinal pigment epithelium mottling in both eyes. Peripheral examination revealed a nonspecific chorioretinal scar in the left eye. Close inspection of the optic nerve in the right eye revealed normal anatomy temporally and marked elevation with a solid appearing mass in the nasal 180°. There was partial obscuration of the vessels and were no apparent hemorrhages. The optic nerve in the left eye demonstrated a similar appearance but with 360° of marked elevation. No spontaneous venous pulsations were observed in both eyes. The cup-to-disk ratio was 0.3 and irregular in the right eye, and was obscured in the left eye.

Given her clinical findings and history of chronic lymphocytic leukemia, a neoplastic infiltrative process of the optic nerves was suspected. As such, dedicated imaging of the optic pathway and brain was obtained. The radiographic workup also assisted in ruling out a compressive mass lesion. A full-body computed tomography scan and lumbar puncture were obtained to rule out metastatic disease. The differential diagnosis also included common etiologies, such as syphilis, sarcoidosis, Lyme disease, *Mycobacterium tuberculosis* (tuberculosis), and anterior ischemic optic neuropathy. Serology to assess for these conditions was obtained and further in-office ancillary testing, including fluorescein angiography and optical coherence tomography, was recommended. The patient received a neurology consultation, and a lumbar puncture was obtained.

Owing to previous pacemaker placement, the patient was unable to undergo magnetic resonance imaging. Therefore, computed tomography scans of the head and orbits with contrast were obtained, which revealed no significant pathologic assessment of the optic pathway or brain. Serology was negative for syphilis, Lyme disease, tuberculosis, and arteritic anterior ischemic optic neuropathy. A complete blood count revealed an elevated leukocyte count of $70.8 \times 10^3/\mu L$ (normal, $3.6–11.1 \times 10^3/\mu L$). Cerebrospinal fluid analysis from the lumbar puncture demonstrated elevated

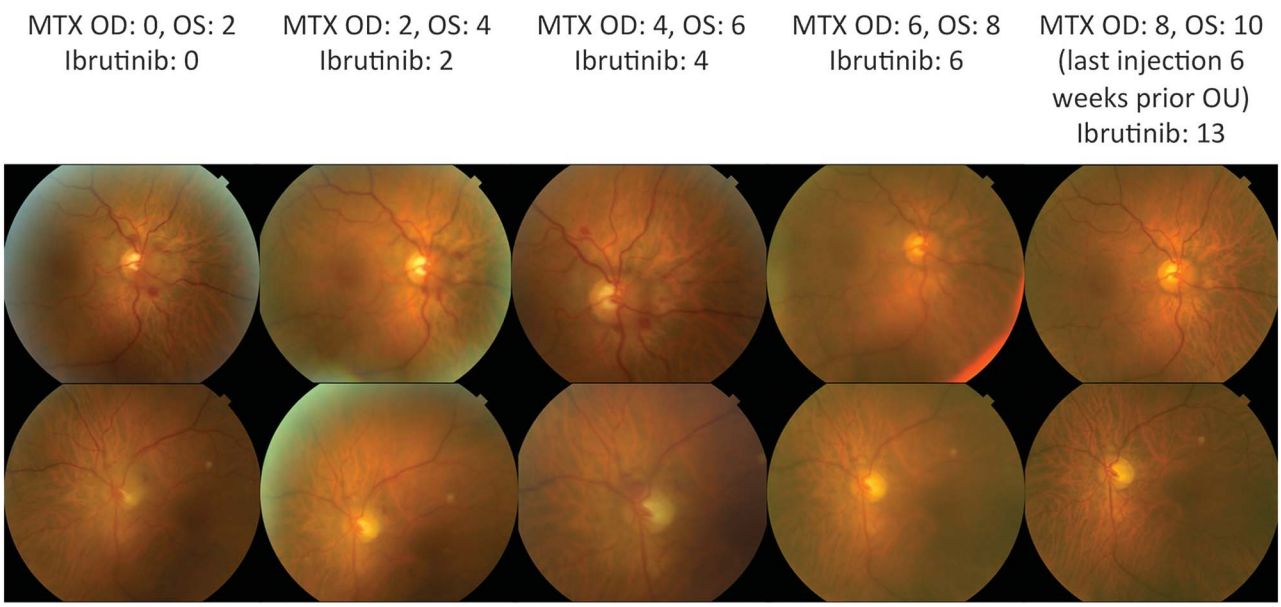

Fig. 2. Serial fundus photographs revealing the improvement in optic nerve infiltration and appearance over time in the right eye (top row) and in the left eye (bottom row). Significant regression of the optic nerve lymphoma was noted in the left eye after two MTX injections and before initiation of ibrutinib (bottom left image). The number of previous intravitreal MTX injections and consecutive weeks of systemic ibrutinib chemotherapy is annotated above.

lymphocyte counts but no malignant cells. The full-body computed tomography showed an enlarged left axillary node, which was subsequently biopsied. The biopsy demonstrated zonular lymphoid proliferation consistent with a B-cell lymphoproliferative disorder and was sent for immunohistopathological analysis.

Flow cytometric analysis and fluorescent in situ hybridization were preformed. Cytometric analysis was negative for CD3 or CD43 staining, thus weighing against a T-cell pattern but showed BCL1 positivity. The fluorescent in situ hybridization assay demonstrated positivity for the t(11;14) IGH-CCND1 fusion gene. The immunohistopathological biopsy profile was reviewed by a series of pathology experts and the results were believed to be most consistent with CD5-negative MCL.

Approximately 2 weeks after hospital discharge, the patient presented to our office for further assessment. Her vision measured 20/40 Snellen acuity in the right eye, and counting fingers at 3 feet in the left eye. The anterior and posterior segment findings were essentially stable from previous inpatient examination, and the absence of anterior or posterior segment cell response was confirmed. The optic nerve revealed normal-appearing anatomy temporally but nasally demonstrated a solid-appearing mass within the nerve matter in the right eye (Figure 1A). The entire optic nerve was engulfed with a solid mass in the left eye (Figure 1B). Peripapillary hemorrhaging was also noted in both eyes. Fluorescein angiography revealed late staining of the optic nerves in both eyes (Figure 1, C–F).

While waiting for initiation of systemic chemotherapy, the patient received a series of 400 μg/0.1 mL MTX intravitreal injections. She elected to proceed initially with weekly unilateral injections in the left eye, given the more profound vision loss, optic disk infiltration, and unknown efficacy of MTX therapy for MCL. Intravitreal delivery of MTX is a non-labeled use of this medication. After 2 weeks of intravitreal therapy in the left eye, there was improvement in the temporal disk margin with regression of the infiltrative process (verified by comparative color fundus photography) and no appreciable toxicity. Given the early evidence of clinical efficacy and excellent tolerance, she elected to receive bilateral injections. After initial two intravitreal MTX injections in the left eye and just before the start of intravitreal MTX injections in the right eye, her oncologist started her on systemic ibrutinib 140 mg initially and the dose was gradually increased to 420 mg daily over the next few weeks. A total of 10 weekly injections in the left eye and 8 weekly injections in the right eye were administered over a 10-week period. The response to this regimen was assessed with visual acuity testing, serial funduscopic examinations, and optical coherence tomography analysis.

Her vision was fairly stable between 20/30 and 20/60 in the right eye for the 10-week duration of therapy and ranged between the counting fingers level and 20/400 in the left eye. The patient showed mild signs of MTX keratopathy after the tenth injection in the left eye and eighth injection in the right eye, which was treated with aggressive topical preservative-free lubricating eye drops. This regimen promptly restored vision in each eye to baseline levels. Owing to the marked improvement in optic nerve infiltration and resolution of retinal hemorrhages, the MTX injections were held at that time in favor of weekly surveillance. Clinically, the optic nerves demonstrated steady incremental improvement with each MTX treatment and with eventual ibrutinib therapy over the 10-week duration of therapy (Figure 2). A mild amount of residual nasal disk infiltration in both eyes was present at the 10-week point and remained stable 6 weeks after MTX treatment (Figure 2). During this period, the patient continued to receive systemic ibrutinib therapy. Her vision at this time measured 20/40 in the right eye and 20/400 in the left eye.

Optical coherence tomography analysis throughout her clinical course was performed only on select visits because of limited examination quality from media haze. Baseline pretreatment optic nerve optical coherence tomography revealed diffuse irregular thickening of the optic nerve primarily involving the nasal disk margin in the right eye and diffuse thickening involving essentially the entire disk in the left eye (Figure 3). Over the following 6 weeks, the optic disks demonstrated significant

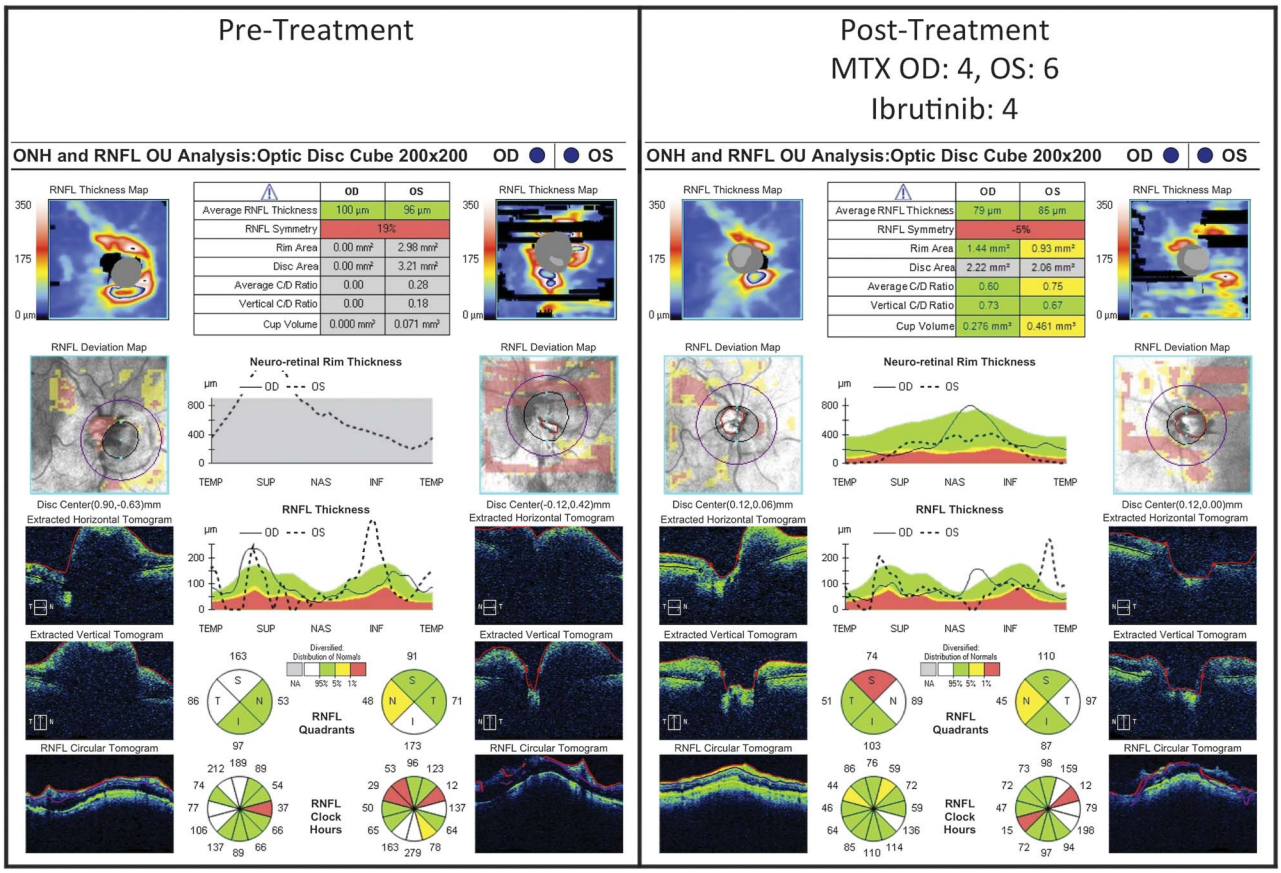

Fig. 3. Optical coherence tomography images of the optic nerves pretreatment (left) and posttreatment (right), after 4 MTX intravitreal injections in the right eye (OD) and 6 in the left eye (OS) in addition to 4 weeks of systemic chemotherapy with ibrutinib. Media haze resulting in inferior image acquisition limits the accurate comparison of retinal nerve fiber layer thickness averages. Nevertheless, the horizontal and vertical tomograms clearly demonstrate regression of the abnormal optic disk thickening over time with restoration of the optic disk cups.

improvement with marked normalization in thickness and contour in both eyes best represented on horizontal and vertical tomographical scans (Figure 3).

Discussion

Patients with mantle cell lymphoma frequently have involvement of the lymph nodes, spleen, liver, bone marrow, blood, and the gastrointestinal tract at the time of presentation.[2] Rarely, central nervous system metastasis is present, occurring in less than 5% of cases.[2] Intraocular involvement is an exceeding rare complication. Despite recent advances in chemotherapeutic regimens, the condition is generally regarded as incurable.[2,3] Patients often demonstrate only short-term responses to treatment and have a high relapse rate.[2]

The genetic alterations underpinning the development of MCL are the translocation t(11;14)(q13;q32) and overexpression of CCND1.[3] These modifications cause aberrant regulation of the cell cycle, therefore allowing the potential for MCL proliferation. Mantle cell lymphoma cells often are CD5 positive and frequently express B-cell–associated antigens.[2] BCL1 (Cyclin D1) positivity is strongly associated with all types of MCL.[2]

Treatment of systemic MCL generally involves combination chemotherapy, but there is no standardized first-line regimen.[2] Newer generation chemotherapeutic agents, such as ibrutinib, have demonstrated great promise in improving survivability. Ibrutinib is a novel Bruton tyrosine kinase inhibitor approved in the United States for treatment of MCL since 2013. A recent Phase 3 clinical trial in patients with relapsed or refractory MCL revealed a significant improvement in median progression-free survival in patients receiving ibrutinib (14.6 months) compared with those receiving conventional therapy with intravenous temsirolimus (6.2 months).[1]

This case report is the first to describe bilateral optic nerve MCL infiltration, to our knowledge. Intraocular MCL is an exceptionally rare manifestation and has only been reported in six cases in the medical literature.[4–9] Patients presenting with intraocular

MCL have heterogeneous clinical findings, including uveal infiltration of the iris and choroid, conjunctival infiltration, anterior uveitis, iris neovascularization, hyphema, vitritis, and orbital infiltration.[4–9] Treatment in these cases has included topical and/or systemic corticosteroids, external beam radiation, and intravitreal and systemic chemotherapy.[4–9]

In our case, the patient received two weekly intravitreal MTX injections in the left eye before her initiation of systemic ibrutinib, as advised by her oncologist. During this initial period of monotherapy in the left eye, the patient demonstrated a mild degree of clinical improvement as noted by her optic nerve appearance. The optic disk in the left eye demonstrated regression of the lymphomatous infiltration with no further development of hemorrhages. The optic disk in the right eye, however, continued to develop new peripapillary hemorrhages without change in the degree of infiltration. Once the treatment regimen was combined with systemic ibrutinib and bilateral MTX injections, a prompt clinical response was observed in the appearance of the optic nerves (Figure 2), visual acuity testing, and subjectively by the patient. Taking into account the majority of the lymphomatous regression occurred with combination treatment, the precise contribution and efficacy of systemic ibrutinib or intravitreal MTX individually in the treatment of this case could not be determined. Nevertheless, the results observed during the short-term MTX monotherapy in the left eye suggest some degree of independent efficacy.

In summary, intravitreal MTX injections may represent a viable treatment option for intraocular MCL. Coordinated care and follow-up with an oncologic specialist is recommended, as systemic chemotherapy still remains the mainstay treatment for metastatic disease. Combination therapy with the latest systemic chemotherapeutic agents, such as ibrutinib, in addition to local intravitreal therapy offer hope for improved clinical outcomes, visual functioning, and survivability in patients diagnosed with metastatic intraocular MCL.

Key words: mantle cell lymphoma, optic nerve lymphoma, intravitreal methotrexate, intraocular lymphoma, ibrutinib.

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