LETTER TO THE EDITOR

To The Editor

Bilateral Infiltrative Optic Neuropathy of Systemic Mantle Cell Lymphoma

Keywords: Infiltrative optic neuropathy, Central nervous system lymphoma, Orbital radiation

We describe a unique case of a patient with known stage IV mantle cell lymphoma (MCL) who presented with bilateral onset of blurry vision and was found to have swollen optic nerve heads with hemorrhages on funduscopy. Neuroimaging demonstrated bilateral perineural enhancement of the intra-orbital optic nerves and leptomeningeal enhancement around the frontal lobes. Infiltration of optic nerves by MCL was presumed to be the culprit and treatment with radiotherapy (RT) to the orbits commenced. After five RT treatments, there was dramatic improvement in visual function and optic nerve head swelling in each eye. This case documents rapid improvement of infiltrative optic neuropathy caused by Non-Hodgkin's lymphoma (NHL) after treatment with orbital RT alone and is only the second case describing infiltration of optic nerves by MCL.

A 70-year-old man was diagnosed 4 months ago with stage IV MCL, blastoid variant, with central nervous system (CNS) involvement based on cerebrospinal fluid analysis which demonstrated protein of 0.42 g/l and $101 \times 10e^6$/l white blood cells with blast morphology consistent with CNS involvement by MCL. He had completed four out of six cycles of chemotherapy with bendamustine and rituximab. He also received three out of four cycles of high-dose intravenous methotrexate (MTX) and intrathecal cytarabine for CNS disease. Ten days after the last cycle of MTX and cytarabine was administered, he complained of headaches accompanied by blurry vision in both eyes. He denied all symptoms of increased intracranial pressure and giant cell arteritis. When examined 5 days after the onset of visual symptoms, best corrected visual acuity was 20/40 in the right eye (RE) and 20/200 in the left eye (LE). There was a left relative afferent pupillary defect. Anterior segment examination was normal. On dilated fundus examination, there was obvious bilateral optic nerve head swelling with hemorrhages (Figure 1A). Humphrey visual fields (24-2 algorithm) demonstrated diffuse depression in each eye (a mean deviation of −29.94 db in the RE and −28.12 db in the LE) (Figure 1C). Urgently performed magnetic resonance imaging (MRI) of the brain and orbits with gadolinium demonstrated new leptomeningeal enhancement around the frontal lobes and bilateral perineural enhancement surrounding the optic nerves (Figure 2). Bilateral infiltration of the intra-orbital portion of optic nerves by MCL was suspected and 6 days after the onset of the visual loss, treatment with whole brain RT, which included the orbits, delivering a total of 20 Gy over five fractions was administered (Figure 3). Treatment with ibrutinib (small molecule binding to Bruton's tyrosine kinase receptors on the surface of B-cells inhibiting cellular adhesion and migration and stimulating apoptosis of cancerous B-cells) for progressive CNS disease was started at the same time as well. When examined 7 days after the last RT session, visual acuity improved to 20/30 in RE and 20/50 in LE and fundus exam demonstrated marked improvement of optic nerve head swelling in each eye (Figure 1B). There was dramatic improvement on formal visual field performance in both eyes seen 2 weeks after completing RT (Figure 1D). When examined 4 months later, central visual acuity and peripheral visual fields have remained unchanged.

MCL is a rare subtype of non-Hodgkin B-cell lymphoma (NHL) representing only 3–10% of all NHLs and usually involving the reticuloendothelial system including blood, liver, spleen, bone marrow, and the gastrointestinal tract.[1] The median age at diagnosis is 65 with a strong male predominance.[2] It has a very poor prognosis with an overall survival of only 4–5 years from the time of diagnosis.[2] CNS involvement in MCL is uncommon and is present in 4–26% of cases.[3]

Although ocular adnexal involvement in MCL is present in 2–7% of patients,[4,5] intraocular involvement is very rare and has only been reported eight times in the English literature. All of the reported cases involved the uvea, presumably because of its rich blood supply, with the iris being the most commonly involved site followed by choroid and ciliary body with variable degree of anterior chamber and vitreous involvement. Optic nerve infiltration by MCL has been described in only one other case previously.[6] When MCL spread involves anterior chamber, vitreous or anterior uvea or if there is peri-orbital involvement, confirmation of the diagnosis using histopathological and cytological studies is relatively straightforward. However, in cases of isolated optic nerve infiltration as was the case in our patient, the histological confirmation is impossible without biopsy of the optic nerve which is usually reserved only for cases of complete visual loss. Our patient had an established diagnosis of MCL with CNS spread with the new onset of isolated optic nerve head swelling and avid perineural enhancement of both intraocular optic nerves on imaging, without involvement of any other ocular structures. Thus, the diagnosis of infiltrative process by known MCL was assumed. It is possible that poor CNS penetration of rituximab has contributed to CNS "sanctuary" of MCL and relapse of the disease despite the systemic and intrathecal therapy at the time of initial diagnosis.

There is no universally accepted treatment for optic nerve infiltration by NHL; however, most patients are treated with radiation therapy in addition to intrathecal chemotherapy, intravenous chemotherapy, and/or high-dose intravenous steroids. RT has been shown to provide rapid although transient improvement in the patients with CNS recurrence of NHLs and our case attests to the rapid improvement of optic neuropathy following RT, although treatment with ibrutinib was administered at the same time as RT.[7] Intravitreal MTX has also been used for treating intraocular spread of MCL.[8] In the only other case in the literature describing optic nerve infiltration by MCL, weekly intravitreal injections with MTX in each eye were used in addition to systemic treatment with ibrutinib.[6] There was only limited improvement of vision after 10 weeks of treatment which the authors hypothesized was due to delayed presentation of patient (3–4 months after onset of visual loss). In our case, radiation therapy to the orbits has resulted in dramatic improvement of vision, demonstrating effectiveness of this therapy for optic nerve infiltration by NHL. Visual improvement was sustained at last follow-up 3 months after initial presentation.

https://doi.org/10.1017/cjn.2020.28 Published online by Cambridge University Press

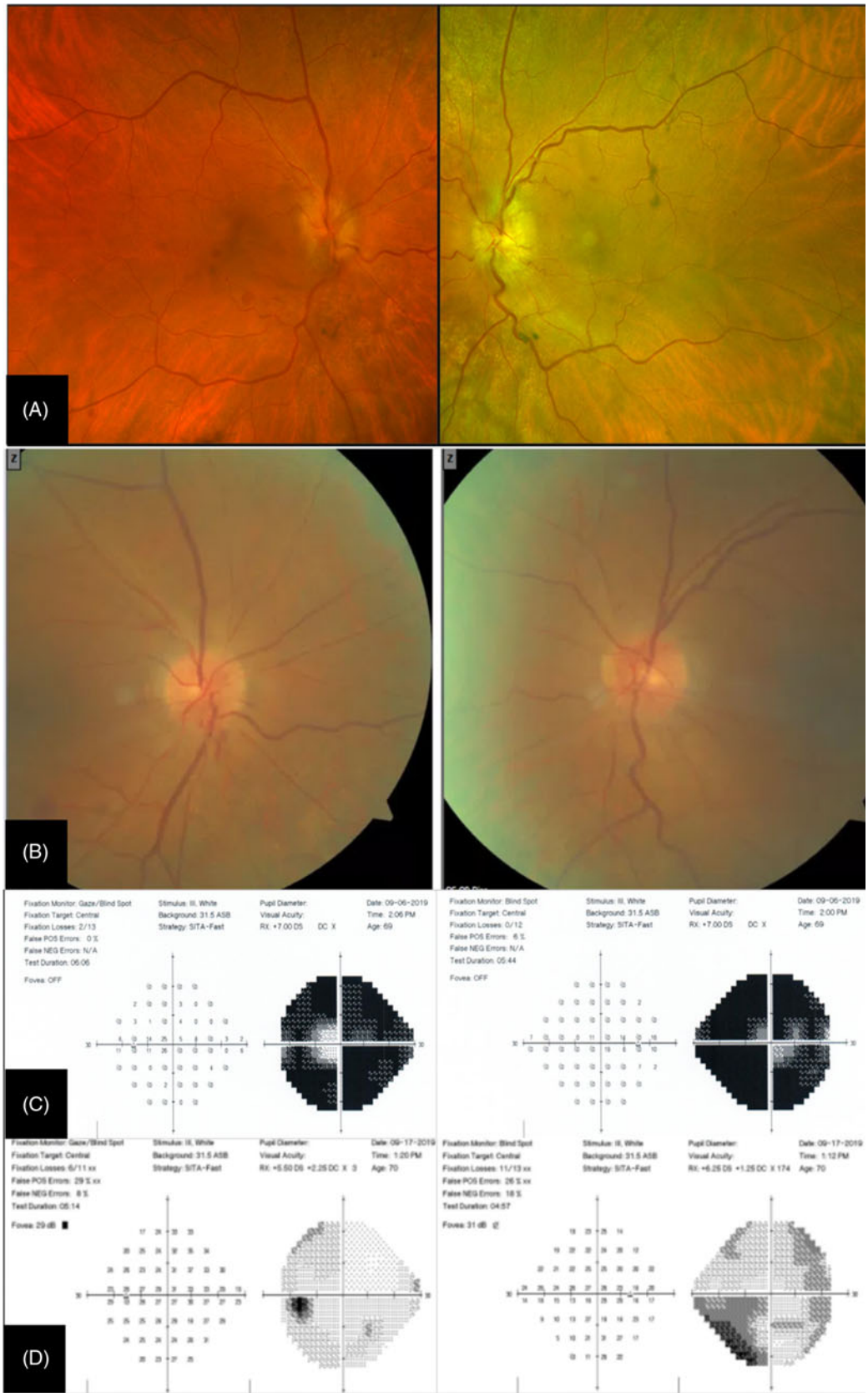

Figure 1: *(A) Fundus photos at presentation demonstrating bilateral optic nerve head swelling with hemorrhages; (B) fundus photos 2 weeks after RT showing marked improvement of optic nerve head swelling in each eye; (C) Humphrey visual fields (24-2 algorithm) demonstrating initial severe bilateral constriction; (D) visual fields 2 weeks after completion of RT demonstrating dramatic improvement.*

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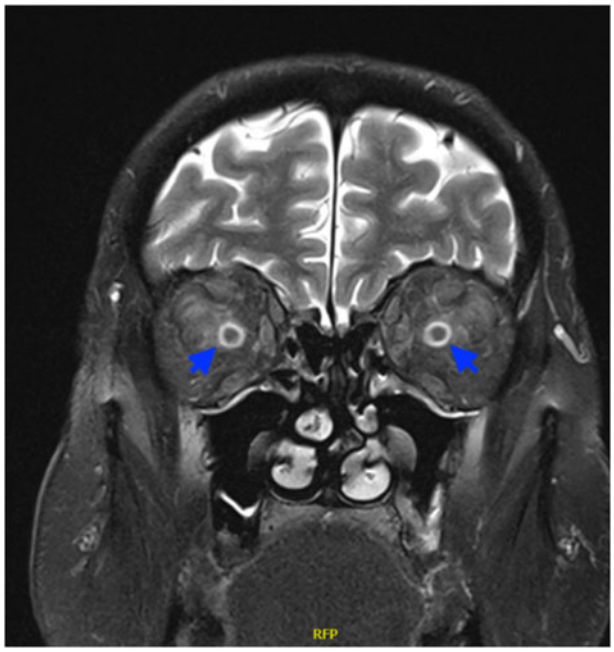

Figure 2: *MRI (T2-sequence with fat suppression and gadolinium) demonstrating perineural enhancement of both optic nerves.*

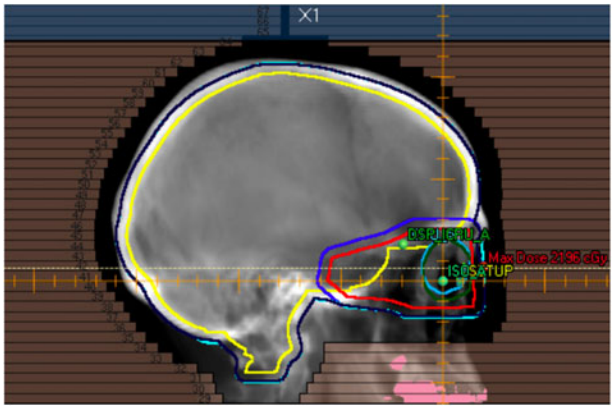

Figure 3: *Screenshot of the radiation treatment field.*

Intraocular involvement by lymphoma should be suspected in any patient with known history of NHL, including its rare variants such as MCL, who are presenting with uveitis, structural abnormalities in any of the uveal structures, or with optic neuropathy. Low-dose RT should be considered as a treatment choice for patients with infiltrative optic neuropathy secondary to NHL as it is safe and has been shown to be effective if administered early after the onset of visual symptoms. Irrespective of the method of treatment, early diagnosis and treatment is the key to restore vision and maintain good quality of life.

Disclosures

The authors have no conflicts of interest to declare.

Statement of authorship

SA: manuscript preparation and revision, data acquisition. TJ-P: manuscript preparation and revision. EM: concept and design, manuscript preparation and revision, data acquisition.

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https://doi.org/10.1017/cjn.2020.28 Published online by Cambridge University Press