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Case Report

Radiotherapy as Salvage Treatment in Intraocular Lymphoma: A Case Report

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Abstract
A 67-year-old previously healthy woman presented with progressive visual impairment including bitemporal hemianopsia. A brain magnetic resonance imaging revealed a contrast-enhancing mass in the optic chiasm, spreading along the left optic tract. The patient underwent a transcranial biopsy of the left optical tract that yielded a diagnosis of diffuse large B-cell lymphoma. CT scans of the chest, abdomen, and pelvis, PET-CT, and bone marrow biopsy revealed no evidence of systemic lymphoma. Thus, the final diagnosis was of primary central nervous system lymphoma of the optic chiasm. Systemic treatment was initiated with full response. Six months after the end of the treatment, recurrence at cerebellum parenchyma and left tentorium was recorded. A new systemic treatment achieved full response. A second recurrence was noted in an optical coherence tomography of the right eye, 2 years after the initial diagnosis. The patient was treated with intravitreal methotrexate with initial success, but eventual failure after 10 months. Intravitreal rituximab was used with no effect. The patient was then referred to radiotherapy and underwent external beam radiotherapy with VMAT. There were no acute toxicities to report. After the radiotherapy treatment, at 1-year follow-up, the patient has no evidence of disease. Long-term toxicities were recorded and are considered manageable. The present case emphasizes the role of ocular irradiation as an option in the management of intraocular lymphoma patients, including in the salvage setting, with an acceptable ocular toxicity profile.

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Introduction

Anterior visual pathway lymphoma can occur as a primary intraocular lymphoma (PIOL), as an intraocular lymphoma (IOL) associated with a primary central nervous system lymphoma (PCNSL) or as a secondary IOL which derives from a systemic lymphoma [1]. PIOL may present independently, prior or subsequent to central nervous system (CNS) involvement [2].

The incidence of PCNSL is 0.28% per 100,000 persons per year in immunocompetent patients [3, 4]. In these patients, ocular involvement occurs in 15–25% of cases, and 80% of these have bilateral involvement [5, 6].

The prognosis of IOL patients depends on the institution of dedicated ocular therapy in addition to PCNSL therapy; median progression-free survival (PFS) and overall survival (OS) are about 18 and 31 months, respectively. Median PFS was prolonged in patients who received dedicated ocular therapy at 19 months as compared to 15 months in those who did not receive dedicated ocular therapy. However, the addition of dedicated ocular therapy had no impact on OS [7].

The optimal treatment of PIOL has yet to be defined, mainly due to treatment data being limited to small studies and case reports.

Here, we report a case of IOL derived from a PCNSL in an immunocompetent patient, resistant to treatment with intravitreal therapy methotrexate (MTX) and rituximab (RTX) that was successfully salvaged with radiation therapy.

Case Report

A 67-year-old woman presented with decreased vision in both eyes (greater loss in the left eye [LE]), bitemporal hemianopsia and fatigue, with no other symptoms or findings in February 2015. Her past medical history was unremarkable. A brain magnetic resonance imaging (MRI) revealed a mass in the optic chiasm, spreading along the left optic tract with homogenous contrast enhancement. Blood tests and cerebrospinal fluid (CSF) analysis were normal, and CSF cytology was negative for malignancy. Symptomatic therapy with corticosteroids was initiated achieving clinical resolution of the bitemporal hemianopsia and improving the LE best corrected visual acuity (BCVA) from 6/30 to 20/40. The patient underwent a transcranial biopsy of the left optical tract, and microscopic examination revealed a lymphoid cell infiltrate composed of predominantly medium to large cells with irregular hyperchromatic nuclei and scant cytoplasm in the background of smaller more monomorphic populations of lymphoid cells. Large cells were CD20+, small cells were CD3+. The malignant B-lymphocytes were MUM1+, BCL2+, CD10–, and BCL6–. The findings were compatible with diffuse large B-cell lymphoma of the CNS. CT scans of the chest, abdomen, and pelvis, PET-CT and bone marrow biopsy revealed no evidence of systemic lymphoma. Thus, the final diagnosis was of PCNSL of the optic chiasm.

Treatment with R-MVP (five cycles), RTX (500 mg/m^2), MTX (3,5 g/m^2), procarbazine (100 mg/m^2/day), and vincristine (1.4 mg/m^2) was initiated in March 2015. After three cycles, the patient developed *Pneumocystis* pneumonia with the need of ventilatory support, and the treatment was stopped. A brain MRI showed full resolution of the chiasm lesion, and the patient was maintained in vigilance. In August 2015, a follow-up brain MRI showed an occipital periventricular lesion with contrast enhancement, and no signs of disease at the optic chiasm. No other evidence of disease was found. Treatment with R-MVP was re-initiated to a total of 5 cycles. In November 2015, a brain MRI showed imaging complete response and consolidation treatment (two cycles) with citarabine (3 g/m^2/day) was initiated. The patient maintained imaging follow-up with no evidence of disease.

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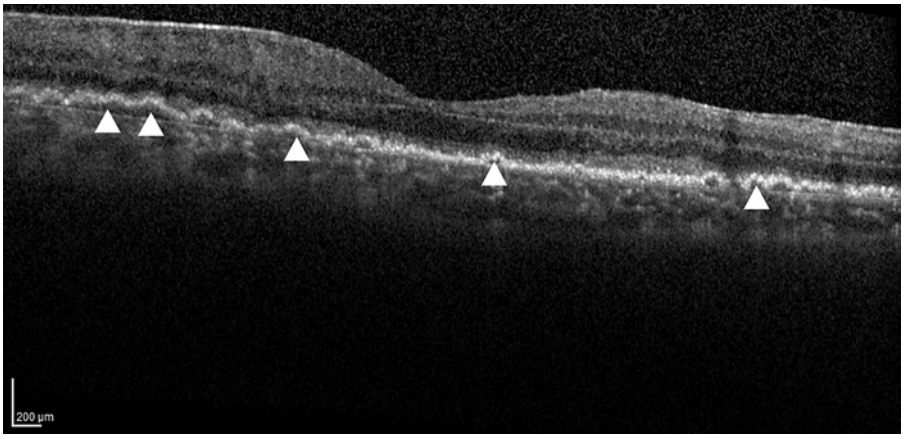

Fig. 1. Ocular OCT after failure with MTX intravitreal injections. Arrowheads point to nodular hyperreflective signals that may indicate lymphomatous infiltrates. RPE disruption has developed into small pigment epithelial detachments.

In July 2016, the patient presented with meningeal signs and headache; CSF analysis revealed a monoclonal B lymphocyte population (CD20+, CD5-) in 0.35% of the sample, and a brain MRI showed contrast enhancement compatible with active disease in the cerebellum parenchyma and left tentorium; no systemic disease was found.

Therapy was initiated (5 cycles) with RTX (500 mg/m^2), MTX (3.5 g/m^2), and alternate weekly intra-CSF MTX (7.5 mg/m^2). Complete remission was achieved in CSF and Brain MRI. RTX (500 mg/m^2) was continued, and in January 2018, after the 10th cycle, there was no macroscopic evidence of disease (CSF, MRI, and PET scan).

In March 2018, the patient complained of photophobia and pain in the right eye (RE). The ophthalmologic examination revealed an anterior chamber cellular reaction (+2 Tyndall), vitritis, and a temporal yellow subretinal plaque on fundoscopy. An optical coherence tomography (OCT) was performed revealing retinal pigment epithelium (RPE) undulation, suggestive of subretinal cellular infiltration (shown in Fig. 1). RE panuveitis was diagnosed, and a vitreous biopsy was performed, revealing NHL B cells. No macroscopic disease was found on a brain and optic tract MRI. The patient continued RTX (500 mg/m^2) until completion of 12 cycles and initiated intravitreal treatment with MTX (400 µg/0.1 mL) bi-weekly (8 cycles), then weekly (4 cycles), and then monthly.

After the first two intravitreal injections, opthalmologic examination was negative for cellular inflammation in both anterior chamber and vitreous, and although the patient developed macular edema, evidence of subretinal infiltration was no longer visible in consecutive OCTs. In January 2019, after 10 monthly cycles of intravitreal therapy, a worsening in the control OCT with RPE undulation, indicated probable disease progression (with no macroscopic evidence on MRI), and the patient was proposed to receive 4 weekly cycles of intraocular RTX (1 mg/0.1 mL).

In April of 2019, patient's BCVA of the RE was 20/50 and LE 20/30 with no cellular anterior chamber reaction but with central vitritis (2+) at fundoscopy and RPE undulation showing no signs of improvement at the follow-up OCT. Because there was no evidence of clinical improvement after intravitreal treatment with RTX, the patient returned to weekly MTX intravitreal injections and was referred to radiotherapy. A new evaluation revealed no macroscopic evidence of disease (CSF and MRI). The patient underwent external beam radiotherapy with VMAT, a total of 24 Gy in 12 fractions was given to both eyes and the optic tract,

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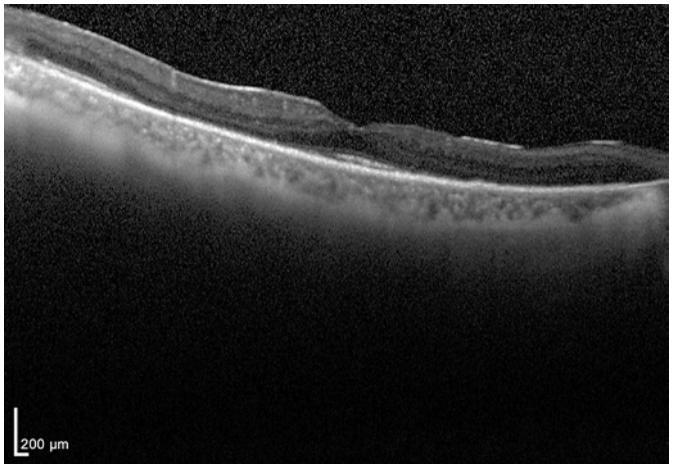

Fig. 2. Ocular OCT after radiotherapy. No subretinal infiltration is present.

a subsequent boost up to 36 Gy in 18 fractions was given to the RE, right optic nerve, chiasm, and right optic tract. There were no acute toxicities related to the treatment.

At 12 months of follow-up, there is no evidence of ocular recurrence (Fig. 2) and a brain MRI also showed no signs of disease. At the last ophthalmologic examination, as a probable consequence of radiotherapy, the patient presented with an RE diffuse superficial punctate keratitis that was managed with ocular lubricant. Her current RE BCVA is 20/100 and LE 20/25. Due to presence of a RE nuclear cataract and refractory macular edema, the patient is scheduled to have RE phacoemulsification surgery with a simultaneous injection of a sustained-release dexamethasone intravitreal implant (Ozurdex®).

Discussion

Given the rarity of IOL, there is a lack of prospective randomized trials that establish a standard therapy. Currently treatment is influenced by disease degree, CNS involvement, and the general performance status of patients [8]. Radiotherapy, chemotherapy, and intravitreal chemotherapy are all available, either used alone or in combination. Retrospective data seems to indicate that treatment of IOL, regardless of CNS involvement should include some form of local therapy, such as intraocular chemotherapy or ocular radiation as this increases disease-free survival in these patients [7].

Some authors have recommended high-dose intravenous MTX, but doubts remain around the concentration of MTX in the anterior chamber due to the limited penetration of systemic chemotherapy into the eye due to the existence of blood-ocular barriers [9]. As an alternative, intravitreal chemotherapy with MTX is nowadays widely used with most reports and case series showing prolonged remission with maintenance of visual function and minimal complications from the injections [1, 10, 11]. MTX can also be used in combination with other medications, such as thiotepa and dexamethasone [1]. Recent reports indicate that the combination of systemic high-dose MTX with intravitreal MTX is associated with a CNS disease-free survival at 2 years of 58.3%, although polychemotherapy is also associated with higher drug toxicity [1, 11]. Intravitreal chemotherapy with 0.4 mg MTX in 0.1 mL, has thus been used in persistent IOL [12]. But drug resistance can arise with prolonged use, as it has probably happened in this case. As an alternative to intravitreous MTX, intravitreal RTX has been used, either to decrease the frequency of treatments with MTX or in MTX-resistant patients [13].

Ocular irradiation has been widely used in IOL, with or without concomitant prophylactic CNS treatment, and doses ranging from 30 to 50 Gy have been reported with rapid improvement of patient's symptoms [1, 9]. Exclusive ocular irradiation toxicities include radiation retinopathy, vitreous hemorrhage, dry eye syndrome, conjunctivitis, neovascular glaucoma, optic atrophy, punctate epithelial erosions, and cataract [1].

In this case, the patient had PCNSL with multiple relapses, treated with systemic chemotherapy. The last relapse was an IOL with no other evidence of disease. Given the favorable toxicities profile, intravitreous MTX therapy was initiated with initial success, but eventual failure. RTX was used as the ocular disease appeared to be MTX resistant, but with no evidence of clinical improvement. The patient was then referred to radiotherapy, with good results in local control, no evidence of disease present in the follow-up examinations and manageable toxicities. The dose used in this patient, up to 36 Gy, is well below the Quantec limits of 55 Gy (<3% of probability of optic neuropathy) for the optical pathways and chiasma, and well below the limits for brain parenchyma of 60 Gy (<3% of probability of radionecrosis) [14].

Although other systemic and intravitreal therapies are associated with less toxicity and should be considered as a first line of treatment, ocular irradiation should be regarded as an option in the management of IOL patients, including in the salvage setting, with an acceptable ocular toxicity profile.

Statement of Ethics

The patient in question has given written informed consent for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Raul Colaço – intern that followed the case during the radiotherapy treatment, drafting of the case report. Mariana Portela – intern that followed the case during the ophthalmological treatment, drafting of the case report. Marta Guedes – medical consultant in ophthalmology who followed the case in ophthalmology, revised the case report. António Mota – medical consultant in radiotherapy who followed the case in radiotherapy, revised the case report.

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