ORIGINAL ARTICLE

Intravitreal methotrexate injection for intraocular lymphoma

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Abstract

Objectives: To review the clinical outcomes of five patients with intraocular lymphoma (IOL) who were treated with intravitreal methotrexate (MTX) injections at the Hong Kong Eye Hospital after 2022.

Methods: We retrospectively reviewed medical records of five patients with definite or presumed IOL without systemic or central nervous system (CNS) involvement at the time of diagnosis, who were treated with intravitreal MTX injections.

Results: In total, eight eyes in one man and four women of Chinese ethnicity aged 54 to 90 (mean, 68.4) years underwent intravitreal MTX injections for IOL. Three patients had primary IOL; one patient had a relapse of diffuse large B-cell lymphoma with secondary IOL; and one patient had a relapse of primary CNS lymphoma with ocular involvement. All five patients underwent diagnostic pars plana vitrectomy. Definitive cytology of malignant large B-cell lymphoma was achieved in only one eye, whereas four eyes were diagnosed cytologically with a lymphoproliferative lesion. All patients received local intravitreal MTX injections with a mean of 20.9 injections given to each eye. All patients achieved ocular disease regression; however, two patients with primary IOL eventually had CNS involvement.

Conclusion: Primary IOL carries a high risk of CNS disease progression. Local ocular treatments such as intravitreal MTX injections can effectively control the disease locally but do not prevent or treat CNS or systemic involvement. Monitoring by a multidisciplinary team using magnetic resonance imaging, positron emission tomography-computed tomography, and/or lumbar punctures can detect CNS or systemic disease early.

Key words: Central nervous system neoplasms; Intraocular lymphoma; Intravitreal injections; Methotrexate; Uveitis

Introduction

Intraocular lymphoma (IOL), also known as vitreoretinal lymphoma, is a rare malignancy that is difficult to diagnose and treat and is associated with high morbidity and mortality. It can masquerade as noninfectious or infectious uveitis or other metastatic neoplasms.[1] A definitive histopathological diagnosis is difficult to obtain.[2] IOL is categorized as either primary (a subset of primary central nervous system [CNS] lymphoma) or secondary (metastasizing to the eye from outside the eye or CNS).[2] The incidence of primary IOL is estimated to be 0.047 per 100 000 people per year and has been increasing in recent decades.[3] Treatment depends on the category and extent of extraocular and systemic involvement. Local ocular treatment options include ocular radiotherapy and intravitreal injections of chemotherapy

such as methotrexate (MTX). Systemic chemotherapy and/or radiotherapy are used for systemic lymphoma.[4] In 2022, intravitreal MTX was introduced as a treatment modality at our hospital. This study reviewed the clinical outcomes of five patients with IOL who underwent intravitreal MTX injections.

Methods

Medical records of patients who were diagnosed with IOL and treated at the Hong Kong Eye Hospital after 2022 were identified using the hospital's electronic database. Presumed primary IOL was defined as eyes with clinical signs, symptoms, and disease course compatible with IOL diagnosed by a vitreoretinal or uveitis specialist, with refractory response to conventional immunosuppressive therapy and at least one involved eye cytologically diagnosed with a lymphoproliferative lesion.

Pars plana vitrectomy for vitreous biopsy was performed according to standard protocols. All patients discontinued topical and systemic corticosteroids and immunosuppressants at least 2 weeks before biopsy to maximize cytological yield. The standard three-port 23-gauge vitrectomy technique was used. An undiluted sample was obtained through aspiration before infusion into a syringe. Both undiluted and diluted samples were preserved with CytoRich Red and cytologically evaluated by pathologists. Adjunct immunocytochemical staining was performed if the samples were adequately cellular. If atypical or malignant cells were detected, the patient was referred to oncologists for systemic examination including magnetic resonance imaging (MRI) of the brain and orbit, whole-body positron emission tomography–computed tomography (PET-CT), and lumbar puncture at the oncologist's discretion.

Treatment comprised 25 intravitreal injections of 400 µg MTX during the induction (twice weekly for 4 weeks), consolidation (once weekly for 8 weeks), and maintenance (once monthly for 9 months) phases for a year.[5] Thereafter, patients were followed up monthly and then 2-monthly if stable, except for those with difficulty attending follow-up visits. Patients were monitored for treatment response (by measuring visual acuity, the presence of vitritis/vitreous cells, and regression of subretinal/subretinal pigment epithelium lesions) and adverse effects (including corneal epitheliopathy and maculopathy, such as cystoid macular edema).

Results

Eight eyes in one man and four women of Chinese ethnicity aged 54 to 90 (mean, 68.4) years underwent intravitreal MTX injections for IOL (**Table**). One patient with bilateral primary IOL who opted for systemic chemotherapy was excluded.

Table. Clinical characteristics and outcomes of five patients who underwent intravitreal methotrexate (MTX) injections for intraocular lymphoma (IOL).

Patient age/sex	Initial presentation	Diagnosis	Time to diagnosis, mo	Pathology	Systemic investigations	No. of MTX injections	Follow-up duration, mo	Outcomes	Visual acuity	
									On presentation	Last follow-up
90/F	Right eye: floaters, exudative retinal detachment and choroidal detachment; both eyes: anterior chamber inflammation, vitritis, and subretinal infiltrates	Diffuse large B-cell lymphoma relapse with secondary IOL	1	Right: hypocellular; left: lymphoproliferative lesion	MRI brain and orbit, whole-body PET-CT were inconclusive for CNS/systemic metastases	19 each eye	29	Both eyes: premature termination of treatment due to cystoid macular edema with no ocular relapse or CNS/systemic metastases	Right: counting fingers; left: hand motion	Right: 0.4; left: 0.4
59/F	Right eye: blurring of vision, refractory vitritis with subsequent subretinal infiltrates; left eye subretinal infiltrates after 9 months	Presumed primary IOL	10	Right: atypical lymphoproliferative lesion; left: acellular	MRI brain, whole-body PET-CT, and lumbar puncture showed no evidence of systemic lymphoma	Right: 25; left: 15	32	Developed CNS lymphoma in the right parietal lobe at 23 months and hence early termination of treatment; no ocular relapse after systemic chemotherapy	Right: 0.4; left: 0.7	Right: 0.1; left: 0.3
69/F	Both eyes: floaters, vitritis, and mild anterior chamber inflammation	Presumed primary IOL	30	Right: lymphoproliferative lesion; left: atypical cells	MRI brain and orbit, whole-body PET-CT showed no evidence of systemic lymphoma	25 each eye	27	No ocular relapse or CNS/systemic metastases	Right: 0.2; left: 0.2	Right: 0.7; left: 0.3
54/M	Right eye: blurring of vision, vitritis with subretinal infiltrates	Primary CNS lymphoma relapse with ocular involvement	1	Lymphoproliferative lesion	MRI brain, whole-body PET-CT, and lumbar puncture showed no evidence of systemic/CNS lymphoma recurrence	23	14	No ocular relapse or CNS/systemic metastases	Hand motion	0.1
70/F	Right eye: blurring of vision, vitritis and subretinal infiltrates	Primary IOL	0.25	Malignant B-cell lymphoma	MRI brain and orbit, whole-body PET-CT, and ultrasonography-guided right neck lymph node biopsy showed no evidence of systemic/CNS lymphoma	16	16	Developed CNS lymphoma in the right basal ganglia at 6 months and hence premature termination of treatment; no ocular relapse after palliative whole-brain radiotherapy	0.1	0.5

Abbreviations: CNS=central nervous system, MRI=magnetic resonance imaging, PET-CT=positron emission tomography-computed tomography

Standard blood tests for uveitis and chest radiographs did not reveal infective causes or systemic rheumatological disorders. One patient with bilateral disease and a history of stage IVa diffuse large B-cell lymphoma was diagnosed as having a relapse with secondary IOL. Another patient with unilateral disease and a history of primary CNS lymphoma of the brainstem was diagnosed with ocular relapse. The remaining three patients were diagnosed as having primary IOL; two had bilateral disease and one initially presented with unilateral disease, which progressed to bilateral involvement 9 months later, despite having received 22 intravitreal MTX injections.

Ocular symptoms included vitritis (100%), subretinal infiltrates or lesions (60%), blurred vision (60%), floaters (40%), anterior chamber inflammation (40%), and exudative retinal detachment with choroidal detachment (20%). The presentations of subretinal/subretinal pigment epithelium lesions varied greatly, ranging from diffuse subretinal infiltrates to a discrete subretinal mass with the classical 'leopard-spot' pattern (**Figures 1 and 2**).

The time to diagnosis ranged from 1 week to 30 months (mean, 8.45 months; median, 1 month). All patients with primary IOL were initially misdiagnosed with infectious or noninfectious uveitis. All the patients with a history of lymphoma or those presented with subretinal infiltrates or lesions were diagnosed within 1 month.

All five patients underwent pars plana vitrectomy and vitreous biopsy. One eye in a patient with unilateral primary IOL was cytologically diagnosed with malignant large B-cell lymphoma. Four eyes were cytologically diagnosed with lymphoproliferative lesions. One eye had undergone pars plana vitrectomy elsewhere, which revealed only atypical cells. MRI of the brain and orbits and whole-body PET-CT results of all patients were negative or inconclusive. Two patients had lumbar punctures, both negative for CNS involvement.

All the eight eyes were treated with intravitreal MTX injections. Each eye received 15 to 25 (mean, 20.9) injections. All eyes achieved ocular disease regression and visual improvement. Three eyes completed the full treatment course, with no IOL recurrence. The most common complication was corneal epitheliopathy, which was treated with bandage contact lenses and lubricants. Three eyes developed corneal epithelial defects, requiring deferral of injections. Two eyes had cystoid macular edema (after 19 injections), which resolved 2 months after treatment ended with no recurrence (**Figure 3**). Due to CNS or systemic involvement, treatment was terminated early for two eyes and replaced with radiotherapy or systemic chemotherapy.

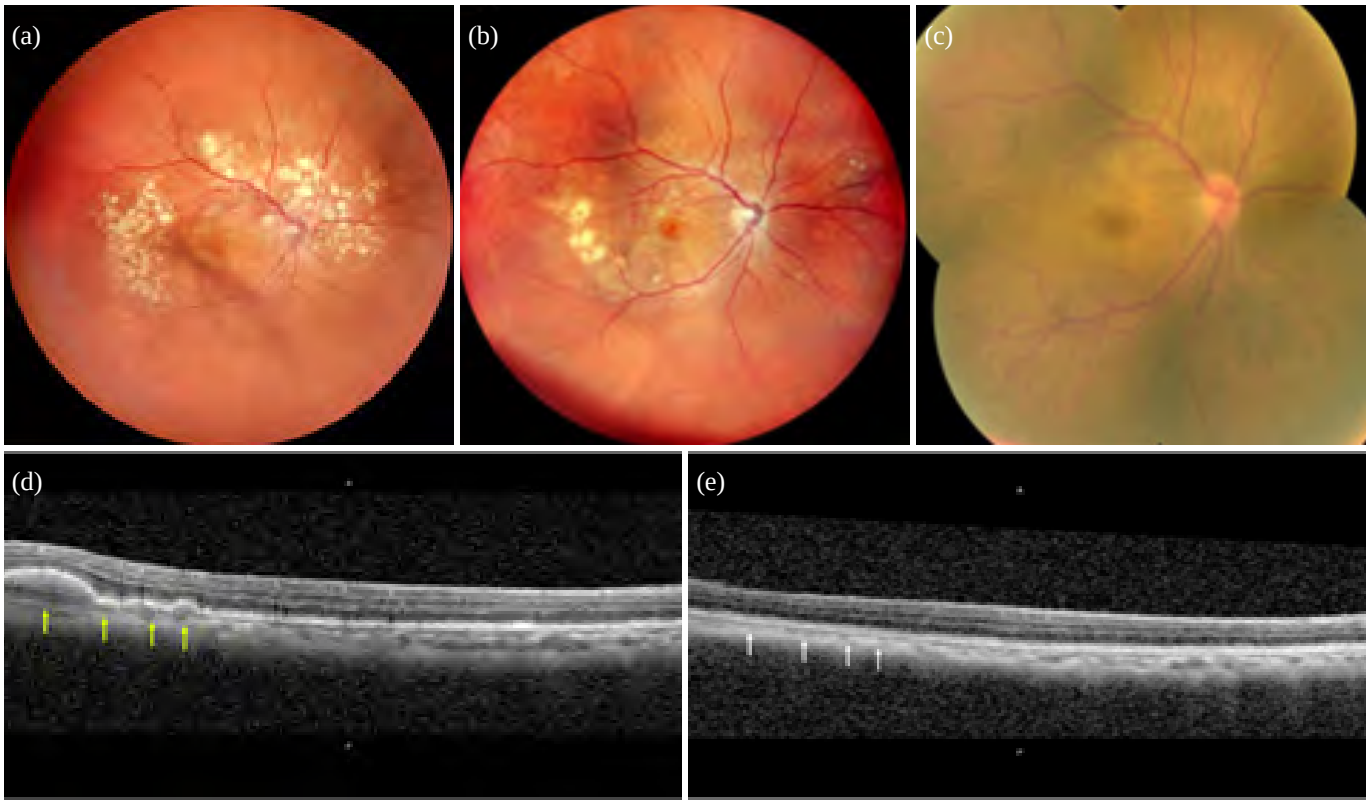

Figure 1. Patient 2: color fundus photographs of the right eye showing (a) subretinal infiltrates with mild vitreous opacities, (b) regression of subretinal infiltrates and resolution of vitreous opacities after two intravitreal methotrexate injections, and (c) complete regression of subretinal infiltrates after 17 injections. Optical coherence tomography of the macula showing (d) hyper-reflective material accumulation (arrows), likely lymphomatous infiltration, in the subretinal pigment epithelial spaces corresponding to the areas of subretinal infiltrates, and (e) resolution of subretinal pigment epithelial infiltrates (arrows) after 24 injections.

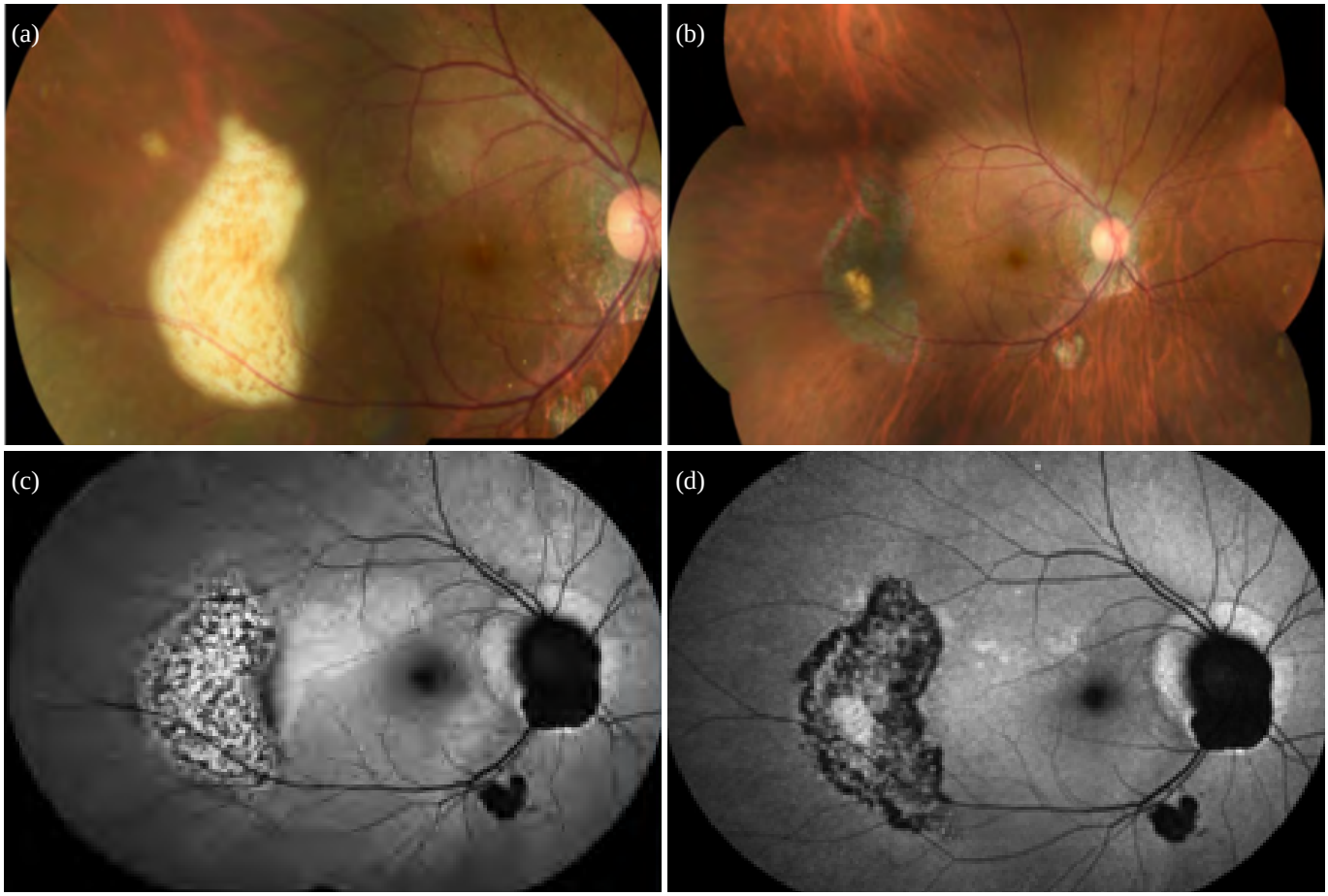

Figure 2. Patient 5: color fundus photographs showing (a) a temporal subretinal mass with 'leopard-spot' pigmentation and (b) regression of the subretinal mass with residual scarring and retinal pigment epithelium changes after intravitreal methotrexate injections. Fundus autofluorescence showing (c) granular hyper-autofluorescence over the mass in the 'leopard-spot' pattern and (d) reduced granularity of hyper-autofluorescence over the mass after injections.

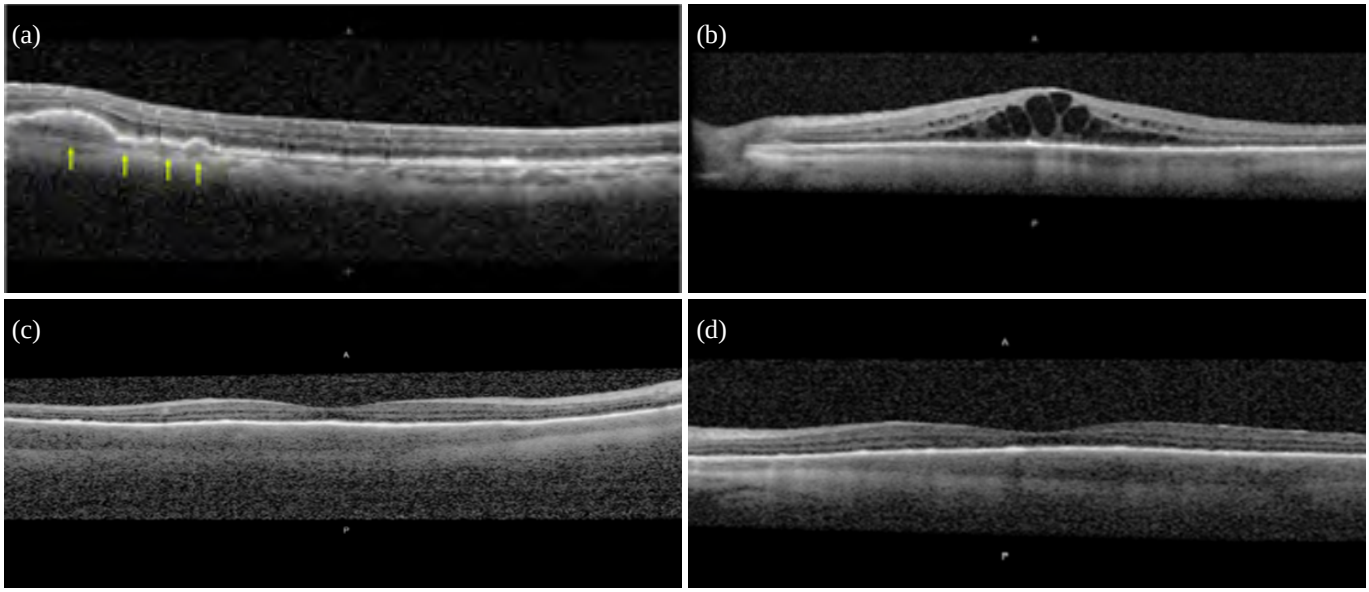

Figure 3. Patient 1: optical coherence tomography of the macula showing cystoid macular edema of the (a) right and (b) left eyes after 19 intravitreal methotrexate injections, and spontaneous resolution of the (c) right and (d) left eyes within 2 months after treatment termination.

After a mean follow-up of 23.6 (range, 14-32) months, all patients were alive. Two patients with primary IOL developed CNS involvement (one after 6 months, the other after 23 months); only one had undergone lumbar puncture with negative cytology. Both patients were diagnosed with diffuse large B-cell lymphoma after brain biopsy. One patient underwent palliative whole-brain radiotherapy, whereas the other received systemic chemotherapy.

Discussion

Previous epidemiological studies of IOL show a mean patient age of 50 to 60 years,[6,7] comparable to our patients. Results of sex predilection have been mixed; [8-10] our findings showed a female predominance with a 4:1 ratio. Bilateral involvement is common, and the most common clinical presentation is vitritis.[7,10,11] The incidence of IOL has increased, potentially due to the growing number of patients with immunodeficiency and/or immunosuppression, increased life expectancy, and advances in diagnostic testing.[1] However, diagnosing IOL remains challenging because it can mimic as infectious or noninfectious uveitis. In our study, all three patients with primary IOL were initially misdiagnosed with either infectious or noninfectious uveitis. Two of these patients were initially treated with topical steroid eye drops and systemic immunosuppressive therapy (one for 10 months, the other for 30 months), with partial clinical response and a refractory clinical course. The patient with the longest time to diagnosis (30 months) had been managed by other ophthalmologists before referral to our hospital after 26 months. The partial response of IOL to corticosteroids or immunosuppressive therapy increases the diagnostic challenge.[1] In our patients, the mean time to diagnosis was 8.45 months, which is similar to or shorter than that reported in other studies.[7,10,12] Ophthalmologists should consider early vitreous biopsy for refractory uveitis cases with suspicious clinical signs such as vitritis and subretinal/subretinal pigment epithelium infiltrates.[13,14]

Ocular imaging, such as optical coherence tomography of the macula (OCT-M), fundus autofluorescence, fluorescein angiography, and indocyanine green angiography, are useful tools for diagnosing IOL. However, clear media are essential to obtain high-quality images for accurate diagnosis. IOL often presents with vitritis, which reduces image quality and diagnostic accuracy. OCT-M was used in all five patients for diagnosis and follow-up. Typical OCT-M findings of IOL include vitreous cells, retinal pigment epithelium nodularity, and outer retinal hyper-reflectivities, which can represent lymphomatous infiltrates.[15] These features may regress with treatment and may be used to monitor disease course and treatment progress.[16,17] Other imaging tools were not routinely used for our patients due to vitritis. In one patient with a large temporal subretinal mass and the 'leopard-spot' pattern, fundus autofluorescence showed granular hyper-autofluorescent spots.[13,14] The increased granularity is associated with lymphoma activity; fundus autofluorescence can be used to monitor treatment response and disease regression.[18]

Cytology remains the gold standard for diagnosing IOL,[19] but obtaining a definitive cytological diagnosis in primary IOL is difficult. Definitive cytology of malignant large B-cell lymphoma could be made in one eye only; four eyes had the cytological diagnosis of lymphoproliferative lesion including primary CNS lymphoma relapse (n=1), diffuse large B-cell lymphoma relapse (n=1), and CNS lymphoma (n=1). The remaining three eyes were hypocellular or acellular and non-diagnostic; one of these had pars plana vitrectomy before being referred to our hospital. Obtaining positive cytological evidence of malignant cells in vitreous biopsy can be challenging because of the sparse number of cells, the presence of confounding features (such as contaminants, debris, fibrin, infiltrating immunoreactive cells, and necrotic or damaged cells), and the use of corticosteroids.[19,20] Previous studies have reported positive cytology in 45% to 60% of vitreous biopsies of IOL.[13,19,21,22] New techniques such as flow cytometry, measuring cytokine levels (such as the IL-10:IL-6 ratio), and molecular examinations can help improve diagnostic sensitivity and specificity.[19] The success rate of diagnostic vitreous sampling can be increased by discontinuing corticosteroids several weeks before the procedure, good communication between the ophthalmologist and the pathologist in handling vitreous samples, and prompt analysis of vitreous samples.[13,19]

All our patients had good disease control and regression as early as after two injections. None received adjunct ocular radiotherapy or systemic chemotherapy for local control. Intravitreal MTX injections can effectively control local ocular lymphoma without serious adverse effects.[23] In our study, the most common adverse effect was corneal epitheliopathy; the incidence of which can be reduced by increasing the intervals between injections.[23] Two eyes in one patient required early treatment termination due to cystoid macular edema, which resolved within 2 months. Other complications include cataract, vitreous hemorrhage, optic atrophy, and sterile endophthalmitis,[5] although none was observed in our patients. In 2022, a Chinese study group proposed a modified treatment protocol with only seven injections over 3 months to reduce complications and treatment burden while maintaining efficacy.[24]

Intravitreal MTX injections alone cannot prevent CNS involvement or treat extraocular systemic lymphoma.[25,26] Approximately 65% to 90% of patients with isolated primary IOL eventually develop CNS disease.[14] In our study, 67% of patients with primary IOL had CNS disease progression. Given the close association between IOL and CNS lymphoma, regular monitoring using MRI of the brain, lumbar puncture for cerebrospinal fluid evaluation, and whole-body PET-CT are necessary to rule out CNS and systemic lymphoma involvement.[13] Patients with CNS and systemic lymphoma involvement require systemic

treatment including chemotherapy and/or radiotherapy. CNS involvement is the leading cause of morbidity and mortality in patients with primary IOL. A European multicenter retrospective study reported significantly lower 5-year cumulative survival rates in patients with primary IOL who developed CNS disease, compared with those who did not (35% vs 68%, p=0.003).[27]

Currently, there are no standard guidelines for treating primary IOL. Some studies recommend the use of systemic chemotherapy, with or without ocular treatment, to prevent and lower the risk of CNS lymphoma development.[28,29] In contrast, a European multicenter retrospective cohort study reported no significant difference in the development of CNS lymphoma in patients with primary IOL who received ocular treatment (including ocular chemotherapy and/or ocular radiotherapy) only, systemic treatment only, or combined treatment.[27,30] The International Primary CNS Lymphoma Collaborative Group's guidelines for primary vitreoretinal lymphoma differ from those of the British Neuro-Oncology Society for managing primary IOL without concomitant CNS disease.[14] The former recommends local intravitreal chemotherapy or ocular irradiation for uniocular disease and either local treatment only or systemic chemotherapy with local treatment for bilateral ocular disease. The latter recommends systemic chemotherapy with high-dose MTX followed by ocular irradiation, with intravitreal MTX injections reserved for isolated ocular recurrences. Given the high risk of CNS disease in patients with primary IOL, regular monitoring, in particular brain MRIs at regular intervals, is recommended for all patients with primary IOL for early detection of CNS involvement.[14,31] There are currently no guidelines for the recommended interval of brain MRI for primary IOL; however, the International Primary CNS Lymphoma Collaborative Group recommendation for primary CNS lymphoma can be taken into consideration: upon completion of treatment, regular MRI scans every 3 months for 2 years, then every 6 months for 3 years, and then annually for 5 years with complete neurological examination and optional lumbar puncture for cerebrospinal fluid analysis if indicated.[32]

Conclusion

IOL is a systemic disease that requires multidisciplinary collaboration involving ophthalmologists, pathologists, physicians, and oncologists. In particular for primary IOL, ocular symptoms may be the first presentation, and ophthalmologists must maintain a high index of suspicion, especially in cases of refractory uveitis. Local ocular treatments such as intravitreal MTX injections are effective in controlling local disease but cannot prevent CNS involvement or treat extraocular systemic lymphoma. Given the high risk of developing CNS disease in patients with primary IOL, good communication with oncologists is essential, as CNS disease progression is the greatest prognostic factor for survival. Regular monitoring of systemic symptoms with neurological examinations, together with regular brain MRIs, PET-CT scans, and lumbar punctures is crucial for early detection of CNS disease and facilitate prompt treatment.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As editors of the journal, CKMC and SKHS were not involved in the peer review process. Other authors have disclosed no conflicts of interest.

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Data availability

All data analyzed in this study are available from the corresponding author upon reasonable request.

Ethics approval

This study was approved by the Hospital Authority Central Institutional Review Board (reference: KC/KE-19-0061/ER-4). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures.

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