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Multimodal imaging in a case of presumed secondary vitreoretinal lymphoma presenting with inner retina and optic nerve head infiltration

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ABSTRACT

Purpose: To report the findings supported by multimodal imaging in a case of secondary vitreoretinal lymphoma presenting with inner retina and optic nerve head infiltration.

Observations: A 64-year-old man with systemic diffuse large B-cell lymphoma presented with reduced visual acuity. Moderate anterior chamber and vitreous cell were present. Fundus exam showed bilateral disc edema and diffuse opaque macular infiltrates with a pseudo cherry-red spot in the left eye. Optical coherence tomography showed inner retinal infiltration and loss of normal architecture. Surgery for tissue biopsy was discussed and declined due to risk. Instead, multimodal imaging and anterior chamber fluid sampling were used as a surrogate for tissue biopsy and helped rule out infectious uveitis and retinal vascular disease. The patient was empirically treated with intravitreal methotrexate with rapid improvement in vision, exam, and quality of life.

Conclusions and importance: Multimodal imaging can support a presumed diagnosis of secondary vitreoretinal lymphoma in order to proceed with intravitreal methotrexate treatment, which can result in rapid clinical and visual improvement.

1. Introduction

Vitreoretinal lymphoma (VRL) is a rare subtype of diffuse large B-cell lymphoma considered to be a variant of central nervous system (CNS) lymphoma. VRL can present as a primary entity isolated to the eye or secondary to an extraocular lymphoma. Intraocular lymphoma is reputed to be a great masquerader and as such can present in a variety of ways, most notably with the appearance of a chronic posterior uveitis.[1,2] Case reports have described VRL masquerading as optic neuritis, retinal vasculitis, acute retinal necrosis and infectious retinitis.[3–7] As such, VRL requires a high level of clinical suspicion and typically relies on ocular fluid sampling for definitive diagnosis. Herein, we report a case of presumed secondary vitreoretinal lymphoma that presented with retinal and optic nerve head infiltration, and was treated with intravitreal methotrexate based on diagnosis with multimodal imaging and anterior chamber (AC) fluid sampling to rule out infectious uveitis, with rapid clinical and visual improvement.

2. Case report

A 64-year-old man presented with a several week history of worsening vision in both eyes. Ocular history was notable for primary open angle glaucoma for which he used dorzolamide-timolol and latanoprost eye drops in both eyes.

Medical history was notable for diffuse large B-cell lymphoma (DLBCL) for which he had completed 4 cycles of R–CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) chemotherapy, type 2 diabetes mellitus, hypertension, and hyperlipidemia. The patient began workup for lymphadenopathy and a 25-pound weight loss 6 months prior to presentation. Initial PET CT imaging revealed numerous hypermetabolic lymph nodes of the neck, chest, abdomen and pelvis; soft tissue nodules in the upper lobe of the left lung; an intensely hypermetabolic spleen; and multifocal abnormal skeletal tracer activity within the axial and appendicular skeleton. Left axillary lymph node biopsy was consistent with DLBCL. Immunohistochemistry was positive for CD20, BCL-2, and BCL-6 with a markedly elevated proliferative index (Ki-67) over 95%. CD10 and Cyclin D1 were negative, and there was only partial C-MYC staining. FISH was negative for IRF4 and MYC

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rearrangements. The patient's cancer was classified as stage IV given the extra-lymphatic involvement with an International Prognostic Index (IPI) of 4 for age, stage, extra-nodal involvement, and elevated serum LDH.

On examination, the patient's best corrected visual acuity was 20/100 in the right eye and 20/70 in the left eye. Intraocular pressure was 9 mmHg in the right eye and 11 mmHg in the left eye. His pupils were both round and equal in size but the right eye demonstrated a relative afferent pupillary defect and was slow to react. His extraocular movements and confrontation visual fields were full.

On slit lamp examination, there was panuveitis in both eyes with 1+ anterior chamber cell and flare, diffuse fine white keratic precipitates, and 1+ vitreous cell in both eyes. View to the fundus in each eye was adequate and fundus exam of the right eye revealed a pallorous disc with mild supranasal disc margin blurring and elevation, and diffuse blot hemorrhages in the posterior pole with an area of whitening in the superior macula that obscured the vessels in some areas (Fig. 1A). The fundus exam of the left eye showed mild disc edema and diffuse retinal whitening of the entire macula with a pseudo cherry red fovea (Fig. 1B).

Optical coherence tomography (OCT) through the areas of retinal whitening in the right superior macula revealed diffuse hyper-reflective infiltrate of the inner retina with loss of architecture (Fig. 1D). At the fovea and remainder of the macula, the OCT showed vitreomacular adhesion, retinal thinning, and loss of outer retinal laminations (Fig. 1C). Left eye OCT was notable for a dense hyper-reflective infiltrate of the inner retina with difficult to interpret outer retina due to shadowing effect (Fig. 1E). OCT of the optic nerves revealed peripapillary extension of the infiltration (Fig. 1F–G). Mid phase fluorescein angiography (FA) of the right eye demonstrated blockage from the observed retinal hemorrhages, with progressive late leakage along the superior arcade vessels and late disc leakage (Fig. 1H–J). FA of the left eye demonstrated extensive diffuse mid and late-phase disc and macular leakage (Fig. 1K-M). Indocyanine green (ICG) was overall normal with only blockage from the observed retinal hemorrhages. B-scan ultrasonography demonstrated vitritis but no apparent retrobulbar lesions.

Magnetic resonance imaging (MRI) of the brain and orbits did not demonstrate evidence of intraconal or intracranial optic nerve infiltration, nor was there abnormal enhancement to suggest intracranial involvement. However, MRI of the spine revealed scattered abnormal enhancing foci concerning for leptomeningeal metastases. Cerebrospinal fluid from lumbar puncture was only notable for elevated protein. The patient received a dose intrathecal chemotherapy with ara-C and hydrocortisone at the time of lumbar puncture and was subsequently started on high-dose methotrexate (HD-MTX) for presumed central nervous system (CNS) lymphoma.

Surgery for tissue biopsy to diagnose secondary vitreoretinal lymphoma was discussed but declined by the patient due to risk and the patient's preference to avoid surgical intervention. Given that the multimodal imaging findings suggested an infiltrative process rather than infective or autoimmune uveitis, the patient elected to start a trial of 0.4 mg/0.1ml intravitreal methotrexate for presumed vitreoretinal lymphoma. An aqueous sample drawn at the time of the first methotrexate injection was negative for herpes simplex virus, varicella zoster virus, cytomegalovirus (CMV), and toxoplasmosis PCR. Serum CMV PCR was also negative. The injection protocol was planned for weekly for four rounds, then every two weeks for four rounds, then monthly thereafter. After the first month of intraocular treatment (4 rounds), the best corrected visual acuity remained 20/200 in the right eye and rapidly improved to 20/25 in the left eye, with corresponding reduction in infiltration OU (Fig. 2A–C), and improvement in both anterior chamber and vitreous cell OU. Vision remained stable at 20/200 and 20/20 respectively after the four injections of methotrexate each spaced two weeks apart (for a total of 8 rounds).

In the interim, the patient underwent four cycles of systemic HD-MTX alternating with Pola-BR (polatuzumab vedotin, bendamustine and rituximab) for relapsed/refractory DLBCL with plans to pursue CAR-T therapy. His clinical course was complicated by pleural effusions status post pleurodesis with talc, chemical pneumonitis, and cardiomyopathy. About 10 days after his 9th round of intravitreal methotrexate, the patient was urgently referred by his cardiologist for a new gaze limitation. He was found to have a right abducens nerve palsy and repeat MRI revealed multiple new intraparenchymal lesions concerning now for intraparenchymal involvement. The patient was admitted for IV dexamethasone and a fifth cycle of HD-MTX. Shortly after discharge, he canceled his appointment for the next round of intraocular methotrexate and it was disclosed that he had been admitted to a hospice center.

3. Discussion

There are several unique features to this case. Notably, the patient was treated for presumed secondary vitreoretinal lymphoma in the absence of a tissue biopsy, which is classically required for definitive diagnosis and to help distinguish from infectious uveitis.[8] Vitreous is the preferred ocular fluid for biopsy and is typically sampled by pars plana vitrectomy, a surgical procedure performed in the operating room under anesthesia, as a vitreous tap with a 25- or 27- gauge needle under topical anesthesia yields an insufficient volume for pathology. Nevertheless, the yield for cytology in a vitrectomy sample is often quite low and requires adjunctive testing of cytokine concentrations eg. elevated IL-10:IL-6 ratio, specific gene mutations such as MYD88 and CD79B, immunoglobulin heavy chain gene rearrangement, and B-cell populations by flow cytometry.[9] Aqueous tap can also be used for sampling with sufficient precision, such as in cases when a hypopyon is present or with advanced PCR analysis.[10–12] In our patient, the main site of involvement was an infiltrate of the macula in each eye. Given the only mild AC and vitreous cell, we discussed the likely low diagnostic yield of anterior chamber fluid or vitreous biopsy alone. The option of retinal biopsy of macular tissue was also discussed, but because of the inherent risk of further central vision loss in either eye, the patient decided against surgical biopsy. A primary retinal vascular disorder was ruled out with FA and a diagnostic AC tap helped rule out infectious uveitis. This allowed for expedited treatment with rapid vision response and improvement in quality of life.

Infiltration of the inner retina is an uncommon presentation of secondary vitreoretinal lymphoma. A recent cross-sectional, multicenter analysis of OCT in 182 eyes with biopsy-proven vitreoretinal lymphoma found sub-RPE infiltrates associated with thickening or detachment of the RPE to be the most common OCT characteristic, seen in 64% of cases, followed by subretinal hyperreflective material, which was found in 43% of cases.[13] Intraretinal lesions extending from the outer nuclear layer as far as up to the nerve fiber layer were found in 7% of eyes, and there were no descriptions of isolated inner retinal infiltrates.[13] Inner retinal hyper-reflective infiltration has been reported more rarely, but typically in conjunction with other sub-RPE findings on OCT.[6,8,14] Jampol and colleagues have described an entity called "vertical hyperreflective lesions'' that are located between the inner layers of the retina and RPE, and hypothesize these represent early microinfiltrates that originate from retinal vessels and capillaries, then infiltrate the retina and down to the sub-RPE space.[15] In the present case, the inner retinal thickening and hyperreflectivity - especially in the setting of the pseudo-cherry red spot in the left eye - was concerning for retinal artery occlusion, which was ruled out by fluorescein angiography. This pattern of infiltration suggests a retinal vascular origin of this patient's vitreoretinal lymphoma; however, it could also represent extension of the optic nerve infiltration into the ganglion cell layer, which perhaps would reflect a different origin. Previous reports have also suggested ocular involvement in DLBCL occurs due to hematogenous spread.[16]

This case also highlights the average disease response to intraocular treatment with methotrexate. There is no established treatment regimen for VRL but a variety of protocols have been reported.[9,17,18] The protocol utilized in this case was weekly injections for four weeks, then injections every two weeks for four cycles, then monthly thereafter. Previous

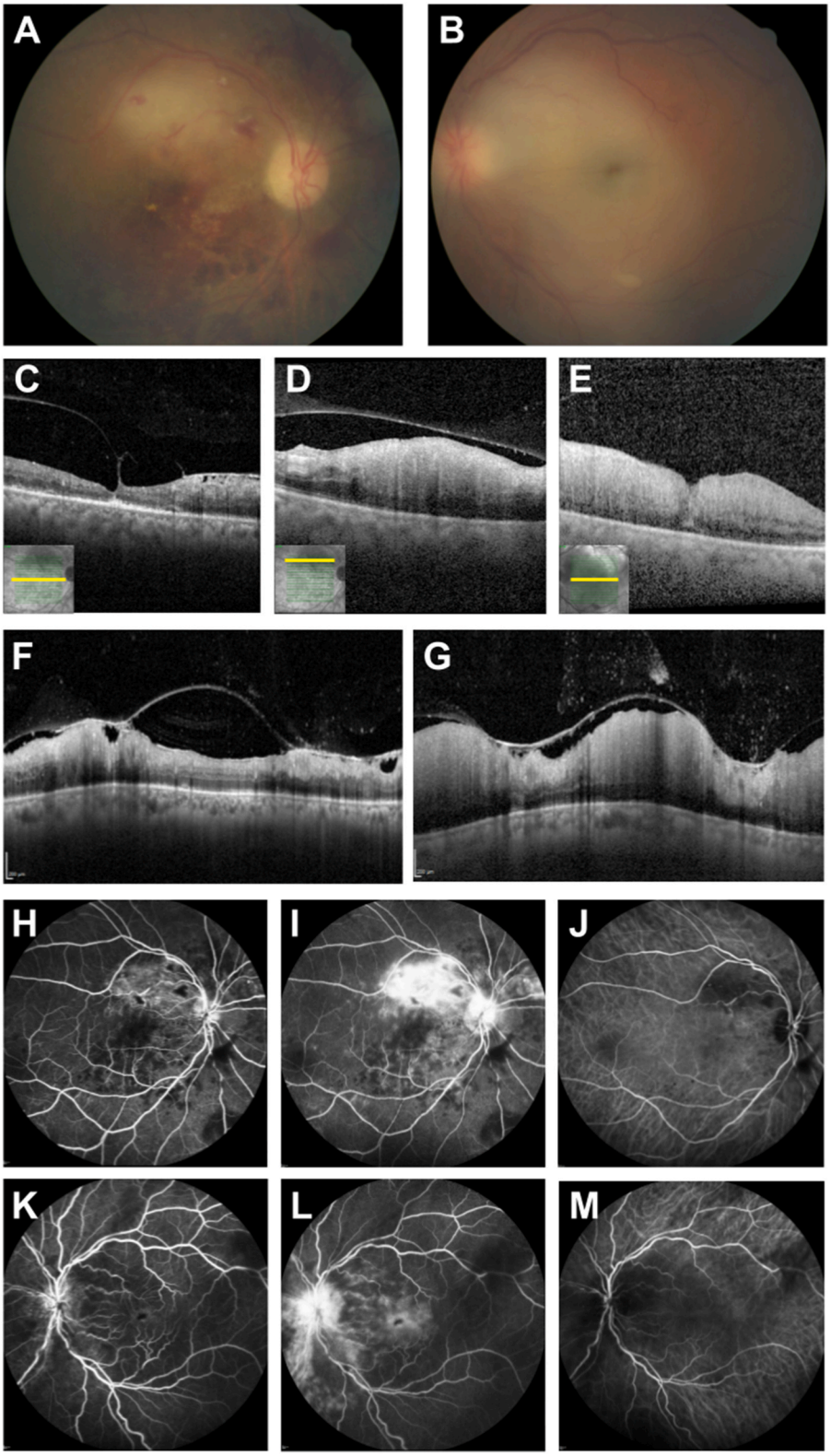

Fig. 1. Multimodal imaging at initial presentation. Color fundus photos show areas of diffuse macular and peripapillary whitening OU and retinal hemorrhages OD (A, B). OCT revealed retinal thinning, loss of outer retinal layer architecture, and vitreomacular traction OD (C) with diffusely thickened hyperreflective inner retinae through areas of macular whitening OD (D) and OS (E). Optic nerve OCT reveals peripapillary extension of infiltration OU. FA of the right eye reveals blockage from retinal hemorrhages and progressive late leakage of the disk and along the superior arcade (H–J), as well as extensive mid and late-phase disc and macular leakage in the left eye (K–M).

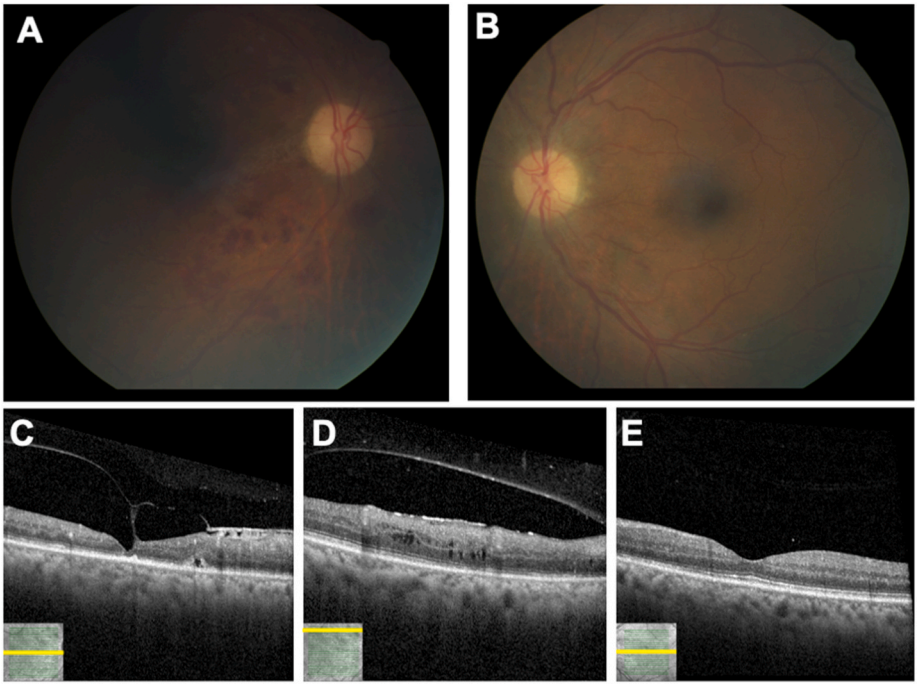

Fig. 2. OCT after first round of intravitreal methotrexate injections. OCT through the fovea of the right eye showed persistent vitreomacular adhesion (A) but there was profound recession of inner retinal infiltration corresponding to areas of macular whitening OU (B, C).

reports have started with intravitreal methotrexate injections twice weekly for four weeks, but our patient had limited transportation to our clinic.[5] Intraocular methotrexate has been shown to produce rapid and significant improvements in vision, though baseline best corrected visual acuity and retinal or subretinal infiltration demonstrate a significant correlation with vision loss.[19–21] In this case, the right eye presented with a vision of 20/100 and persisted post treatment with a vision of 20/200, while the left eye presented with a vision of 20/70 and improved to 20/20 post treatment despite bilateral retinal infiltration. The primary goals of VRL treatment are to preserve visual function and control intraocular disease, as theoretically, the latter can help to eliminate a potential reservoir that could increase the risk of CNS recurrence.[2,9] Combined systemic and intraocular chemotherapy has been shown to yield a higher CNS relapse-free survival but does not seem to affect overall survival.[2,22] In the present case, despite apparently good intraocular disease response and systemic treatment, the patient's disease still progressed with the development of brain lesions, which mirrors the current literature and emphasizes the need for better parameters to assess subclinical disease activity.[5,20]

In summary, this is a case of presumed secondary vitreoretinal lymphoma with a unique presentation of inner retinal infiltration that improved rapidly with intravitreal methotrexate injections.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

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Emily S. Levine: Writing – review & editing, Writing – original draft. **Nikhil N. Batra:** Writing – review & editing, Writing – original draft, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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