Cystoid Macular Oedema as a Presenting Feature of Vitreoretinal Lymphoma

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Established Facts

- Vitreoretinal lymphoma (VRL) initially presenting with cystoid macular oedema (CMO) is rare.
- Causes of CMO in VRL include prior whole brain radiotherapy and chemotherapy as combined modality therapy, epiretinal membranes, and/or intraocular procedures.

Novel Insights

- We report on the case of a patient with VRL who presented with CMO. She had not previously undergone whole brain radiotherapy or any intraocular procedures.
- This case demonstrates that the presence of CMO does not definitively exclude the presence of VRL.

Keywords

Intraocular lymphoma · Macular oedema · Vitreoretinal lymphoma · Primary central nervous system lymphoma

Abstract

A 69-year-old female presented with right vitreous cells and cystoid macular oedema (CMO). One year previously, she had received two cycles of attenuated methotrexate-based chemotherapy for primary central nervous system (CNS) lymphoma, abandoned due to toxicity. There was no past ocular history of note aside from mild cataract. Due to her history of previous CNS lymphoma, we suspected vitreoreti-

nal lymphoma (VRL), but the presence of the CMO made this unlikely. She underwent a diagnostic vitrectomy. Histology and immunohistochemistry showed the presence of a high-grade B-cell VRL.

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Introduction

Vitreoretinal lymphoma (VRL), as opposed to orbital or adnexal lymphomas, is uncommon [1–4]. The exact incidence is unknown [5]. VRL is a high-grade non-Hodgkin lymphoma (usually diffuse large B-cell lympho-

Fig. 1. **a** Optos® red free wide-field fundus imaging of the right symptomatic eye at presentation. Widespread vitreous cells are visible. **b** Optos® red free wide-field fundus imaging of the left asymptomatic eye at presentation. **c** Heidelberg Engineering GmbH ocular coherence tomography and infrared imaging of the right symptomatic eye at presentation showing cystoid macular oedema and subfoveal fluid.

ma) affecting the retina, vitreous, and/or optic nerve [4, 6, 7]. It is considered a subtype of primary central nervous system lymphoma (PCNSL), as opposed to systemic non-Hodgkin lymphoma [4, 7]. VRL can occur prior to, simultaneously, or after the onset of PCNSL. It is estimated that 35–90% of those who present initially with VRL will go on to develop CNSL, 15–25% who present initially with PCNSL will subsequently develop VRL, and 16–34% of cases of VRL present simultaneously with CNS involvement [8, 9].

Diagnosing VRL is notoriously difficult due to the fact that its usual presenting symptoms are often non-specific. Namely, VRL presents with blurred vision in 40–50% of patients, reduced visual acuity in 25–30%, and floaters in 20–25% [10]. Chronic vitreous floaters are common in VRL, leading to it often been mistaken as a chronic posterior uveitis [4, 5]. Creamy orange-yellow subretinal pigment epithelium lesions (solitary or multiple) may be found, and these may be associated with retinal detachment [5, 6]. None of these are specific clinical signs pathognomonic of VRL. Moreover, many ophthalmologists elect to do a central vitreous core tap biopsy rather than sampling the entire vitreous. This is associated with an appreciable false negative rate because lymphoma cells

tend to be concentrated mostly in the outer cortex rather than the core vitreous [11]. These factors all contribute to a delay in diagnosis.

Less commonly, VRL may be associated with iridocyclitis, optic neuropathy, vasculitis, and retinal haemorrhage [4–6]. Cystoid macular oedema (CMO) is rare in VRL [4–6].

Case Report

A 69-year-old female was referred to our tertiary ocular oncology department with a 2-week history of increased floaters and painless reduced central vision in her right eye. The referring ophthalmology department had started her already on preservative-free dexamethasone 1 mg/1 mL (Dexafree®) and ketorolac 0.5% (Acular®) topical therapy.

One year prior to this, she had received dose-attenuated combination chemotherapy (rituximab, high-dose methotrexate, cytarabine) for the diagnosis of primary CNS lymphoma, with multifocal left sided white matter lesions. Chemotherapy was discontinued due to toxicities after two cycles. Radiotherapy was not given due to her age. When she presented with visual symptoms, her CNS lymphoma was thought to be in remission.

On presentation, her best-corrected visual acuities were 6/12 improving to 6/9 with pinhole in her right eye, and 6/9 in the left. She had mild nuclear sclerotic cataracts in both eyes. There were

copious vitreous cells in the right eye with a small degree of CMO and subfoveal fluid (Fig. 1a, c). There were no signs of anterior uveitis, retinal vasculitis, subretinal deposits, or optic disc swelling. The left eye was normal (Fig. 1b).

Due to her history of PCNSL, VRL was suspected. However, on clinical grounds, the presence of the CMO made this unlikely. The differential diagnosis included paraneoplastic vitritis with CMO secondary to recurrent CNSL rather than progression of the disease into the eye. She proceeded to a pars plana diagnostic vitrectomy. Histology revealed highly atypical lymphoid cells (Fig. 2a) associated with eosinophilic lytic debris. This atypical lymphoid population was immunohistochemically positive for CD20, indicating a B-cell phenotype (Fig. 2b). Ki67 showed around 50–60% of the B cells to be in the cycle (Fig. 2c). IgH B-cell monoclonality testing using BioRad 2 primers showed reproducible clones in all 3 reading frames (Fig. 2d). The cytological, immunohistochemical, and clonality findings were diagnostic of diffuse large B-cell lymphoma recurrence in the vitreous.

At her post-operative follow-up, she was found to have new vitreous cells in her left eye. External beam radiotherapy was delivered to both eyes. This provided a slight reduction in her intra-retinal fluid (reduction in central macular thickness by 101 μ m) and cleared the vitreous cells in both eyes. Unfortunately, 6 months after the radiotherapy, she experienced a relapse of both her cerebral and intraocular disease and died shortly afterwards.

Discussion/Conclusion

Cystoid macular oedema in VRL in those that have not been previously treated with radiation or intraocular surgery is uncommon. Cystoid macular oedema in VRL has been reported on previously, but these are found largely in patients who have previously received radiation or intraocular surgery. Cassoux et al. [12] reported in their series that 2 of 81 eyes with VRL had CMO, but 3 eyes in their series had undergone previous pars plana vitrectomy. Velez et al. [13] reported that 6 of 31 eyes with VRL were found to have CMO on fundus fluorescein angiography, but 5 of these eyes had previously undergone intraocular surgery. They did not specify for the 1 eye without previous intraocular surgery whether there had been previous radiation or other intraocular pathology such as an epiretinal membrane [13]. Turaka et al. [14] reported that 3 of 12 eyes with VRL had evi-

Fig. 2. **a** Haematoxylin and eosin-stained cytology preparation showing atypical lymphoid cells. **b** Immunohistochemistry staining with CD20 showing positive staining of the atypical lymphoid cells (brown is positive). **c** Ki67 immunohistochemistry staining the atypical lymphoid cell nuclei. **d** BioRad 2 IgH B-cell clonality testing showing a clonal peak, indicating a monoclonal B-cell population in the vitreous.

dence of CMO on OCT, and 6 of 12 eyes had evidence of CMO on fundus fluorescein angiography, but all patients had undergone either chemotherapy, external beam radiotherapy, or a combination of both for existing systemic lymphoma. Jang et al. [15] found that 2 of 5 eyes with VRL had CMO, but 1 of these eyes had undergone previous pars plana vitrectomy, and the other had pre-existing CNS lymphoma, so one could presume that this patient had already undergone chemotherapy and/or radiotherapy. Recently, Carreras et al. [6] found that 6 of 15 eyes with VRL had presented with CMO, as detected on either fundus fluorescein angiogram or ocular coherence tomography. However, all of these had undergone either previous intraocular surgery or previous combined modality treatment with chemotherapy and whole brain radiotherapy prior to their presentation [6]. Subsequently, Deák et al. [16] published a case of VRL presenting with right CMO and multiple creamy-white subretinal lesions following right cataract surgery. This was treated with intravitreal dexamethasone implant (Ozurdex®). Then, 6 months later his fellow eye developed CMO and was also treated with an Ozurdex implant. The patient was eventually diagnosed with VRL [16]. Despite this patient having CMO at the time of presentation, the right eye had previously been operated on, and cystoid macular oedema-like changes occurring in the unoperated fellow eye following cataract surgery have been described [17].

Our patient had undergone chemotherapy only, without whole brain radiotherapy. She also had not undergone any previous intraocular procedures. Therefore, we concluded that her CMO was a direct result of

her VRL. This case demonstrates that CMO may occur in patients with VRL even when never previously treated with radiation or intraocular surgery.

Statement of Ethics

The subject has been fully anonymised. Written informed consent to publish this case and the images was provided by the patient's next of kin as the patient is now deceased.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Stephanie J. Chiu, Ophthalmology Specialty Registrar – wrote the manuscript including Figure 1. Hardeep Singh Mudhar, Consultant Histopathologist – contributed to all of the histopathological data in the paper, contributed to Figure 2, manuscript revision, and final approval. Beth Harrison, Consultant Haematologist – provided care regarding CNS lymphoma, manuscript revision, and final approval. Kurt Spiteri-Cornish, Consultant Ophthalmologist – provided care regarding the vitreoretinal biopsy, manuscript revision, and final approval. Katharine Sears, Specialty Doctor in Ophthalmology with special interest in Ocular Oncology and Uveitis – provided care regarding vitreoretinal lymphoma, manuscript revision, and final approval.

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