Diagnostic challenges and treatment outcomes of primary vitreoretinal lymphoma in Hong Kong

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Introduction

Primary vitreoretinal lymphoma (PVRL) is a rare and aggressive ocular variant of non-Hodgkin lymphoma (NHL), predominantly of B-cell origin.[1] It represents a subset of primary central nervous system lymphoma (PCNSL), in which malignant lymphocytic cells primarily affect the vitreous and/or retina, with or without involvement of the brain and cerebrospinal fluid. Approximately one-fifth of patients with PCNSL have concurrent ocular manifestations at presentation, whereas 60% to 90% of patients with PVRL develop central nervous system (CNS) disease within 16 to 24 months.[2]

The prognosis for patients with PVRL and CNS involvement is poor, with a median survival of 1 to 2 years.[3] Thus, early diagnosis is imperative for timely treatment. However, diagnosis is often delayed because: (1) PVRL frequently masquerades as chronic uveitis[4]; (2) the diagnostic yield of vitreous samples is often low due to hypocellularity and fragility of lymphoma cells[3]; (3) specialised techniques and experienced cytopathologists are required; and (4) patients often have reservations about undergoing invasive diagnostic vitrectomy.

The current first-line treatment for PCNSL comprises high-dose methotrexate (MTX)–based polychemotherapy, with or without whole-brain radiotherapy. Among patients with isolated PVRL, intravitreal MTX has been shown to achieve ocular tumour control in multiple studies.[4-6] However, there remains no consensus regarding the optimal treatment regimen.

In Hong Kong, NHL is among the top ten cancers in terms of both incidence (2.9%) and mortality (2.6%).[7] Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL globally and locally.[8] Given that more than 95% of PVRL cases are DLBCL,[9] it is important to examine the treatment outcomes of this under-reported disease entity.

Our local experience

We share our experience managing patients diagnosed with PVRL at Prince of Wales Hospital and Alice Ho Miu Ling Nethersole Hospital, Hong Kong, between August 2013 and April 2024.

A case of PVRL was defined by the presence of characteristic vitreous opacity and/or subretinal infiltrate, substantiated by a positive tissue biopsy from the vitreous, brain, or cerebrospinal fluid. In cases without CNS involvement and negative vitreous biopsy, the diagnosis was made by consensus between two vitreoretinal specialists based on clinical examination. Cases of systemic NHL (eg, secondary vitreoretinal metastasis from primary extracranial lymphoma) were excluded. Visual acuity (VA), ocular examination findings, and multimodal ocular imaging of the tumours were recorded. Patient demographics, ocular symptoms, follow-up duration, oncological treatment details, complications, and survival data were collected. Outcomes of interest included initial and final VA and treatment responses. For the latter, an international standardised guideline on ocular responses in PCNSL was utilised[10]: (1) complete response (absence of vitreous cells and resolution of retinal infiltrate [online supplementary Fig a to b of Patient 2 as reference]); (2) partial response (reduced but persistent vitreous cells or retinal infiltrate); (3) progressive disease (increased vitreous cells or progressive retinal infiltrate); and (4) relapse (new lesion in patients who had achieved a complete response).

With ethics approval and waiver of patient consent (The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee, Hong Kong [Ref No.: 2024.175]), 17 eyes from 10 Chinese patients with PVRL were identified, with a median follow-up of 32.5 months (range, 4-86). The majority of patients were women (70%) and the median age at diagnosis was 59 years (range,

52-80; mean, 61.7). Three patients had isolated ocular involvement, and seven had concurrent CNS involvement. Among the latter, ocular involvement preceded CNS disease in four patients (57.1%); CNS involvement preceded ocular disease in three patients (42.9%). The median interval between ocular and CNS involvement was 13 months (range, 4-39). Seven patients had bilateral PVRL, and all affected eyes were symptomatic. Blurred vision was the most common presenting complaint (90%), followed by floaters (30%). The mean VA at presentation was 20/100. The most common ophthalmological finding was vitreous opacity, present in all eyes (100%), followed by subretinal infiltrate in eight eyes (47.1%) and secondary neovascular glaucoma with vitreous haemorrhage in one eye (5.9%) [online supplementary Table 1].

Diagnostic challenges of primary vitreoretinal lymphoma

Primary vitreoretinal lymphoma presents ongoing diagnostic challenges. Its rarity and tendency to masquerade as other ocular conditions can delay diagnosis for up to 21 months.[3,11] Accurate cytopathological diagnosis is further hampered by the intrinsically low volume of vitreous, fragility of lymphoma cells, and hypocellularity.[3] In our series, all 10 patients (14 of 17 eyes) underwent diagnostic and therapeutic vitrectomy (online supplementary Table 2). Among the seven patients with suspicious brain lesions on magnetic resonance imaging, brain biopsy confirmed DLBCL and the diagnosis of PVRL was supported by characteristic vitreous opacity and/or subretinal infiltrate. For the remaining three patients without CNS involvement, diagnosis relied on positive vitreous biopsy findings: (1) cytology demonstrating atypical lymphoid cells; (2) flow cytometry identifying $CD20^+$ B lymphocytes; and (3) polymerase chain reaction revealing monoclonal immunoglobulin heavy locus (IGH) gene rearrangement. Two patients fulfilled these criteria; Patient 10 was diagnosed solely based on clinical evaluation by vitreoretinal specialists (online supplementary Fig c to f). Only seven specimens (50%) yielded positive cytological results with malignant cells and/or atypical lymphoid cells (online supplementary Table 2). Negative or equivocal results do not definitively exclude lymphoma,[9] thus adjunctive cytopathological tests are often required. These include, in decreasing order of sensitivity (as ranked by a recent systematic review)[3]: interleukin (IL) analysis (IL-10–to–IL-6 ratio >1; 89.4%), flow cytometry identifying $CD20^+$ B lymphocytes (88.0%), monoclonal IGH rearrangement via polymerase chain reaction (85.1%), and myeloid differentiation primary response 88 (MYD88) mutation analysis (70%). In our study, flow cytometry was performed in six eyes (42.8%), with only two (14.2%) showing clonal populations. Polymerase chain reaction was conducted in two eyes (14.3%); one (7.1%) demonstrated IGH gene rearrangement. Interleukin analysis was not performed. Flow cytometry and gene rearrangement testing are available in the Hong Kong public healthcare setting; other tests may incur additional charges.[12] A large Chinese case-control study proposed a six-item diagnostic framework for DLBCL-associated PVRL[9] (online supplementary Table 3). They reported that 15% of patients were diagnosed when only criteria 1 to 3 were met. Requiring criterion 1 plus two positive results from criteria 4 to 6 increased diagnostic sensitivity to 97.5%, with 100% specificity.[9]

Several factors may have contributed to the low diagnostic yield of vitreous biopsy in our series. First, all patients received corticosteroids to control ocular inflammation, given that PVRL frequently masquerades as uveitis. This may have induced cytolytic effects on lymphoma cells prior to diagnostic vitrectomy.[13] Second, vitreous biopsy was not repeated in cases with equivocal or negative cytological results, owing to the absence of clinically significant vitreous opacities to justify repeat sampling.[3] Third, additional cytopathological tests require prior arrangement and coordination with on-duty cytopathologists. Sensitive assays, such as IL analysis, could have been performed if preliminary communication had occurred before the vitreous biopsy. Finally, despite standardisation of sampling techniques and procedures, sample hypocellularity limited the yield of clonal lymphoma cells on flow cytometry (2 of 6 eyes), where definitive diagnosis requires a substantial number of viable, intact neoplastic cells.[3] To overcome the challenge of hypocellular vitreoretinal lymphoma tissue samples, the use of cell-free DNA, rather than cellular DNA, to detect MYD88 mutations has been proposed. Notably, detection rates were reportedly 30% higher when cell-free DNA was used,[14] even in aqueous humour samples, which contain minimal cellular DNA. A recent report has further validated this technique in highly diluted (>100-fold) vitreous samples.[15]

Efficacy and safety of intravitreal methotrexate in primary vitreoretinal lymphoma

Before the introduction of intravitreal chemotherapy, external beam radiation therapy was the primary treatment for PVRL. Due to its severe adverse effects, radiation therapy is now generally reserved for patients with bilateral involvement, advanced age, or difficulty attending frequent intravitreal injections.[1] Intravitreal MTX is currently considered the first-line treatment owing to its high efficacy.[1]

To date, no standardised treatment regimen for intravitreal MTX in PVRL has been established—the number of injections required to achieve a

complete response varies widely.[1] While Smith et al[16] proposed a protocol of 25 injections, a 10-year experience reported by Frenkel et al[17] indicated that only 39% of patients were able to complete the treatment due to frailty or death. Notably, a median of five injections (range, 2-11) was sufficient to achieve a complete response. The same group later reported a complete response rate of 97% over a mean (± standard deviation) follow-up of 38 months with as few as five (± four) injections,[4] which subsequently prompted proposals advocating for fewer injections.[6,16] In our study, intravitreal MTX was administered at a dose of 400 μg/0.05 mL weekly. The number of injections was titrated based on clinical response, defined as achievement of complete response, and patient acceptance and tolerance. Ultimately, nine eyes (52.9%) received MTX injections, while eight eyes (47.1%) underwent vitrectomy alone (Table). Methotrexate was not administered in cases where patients achieved a complete response after vitrectomy and declined invasive treatment, experienced intolerance (Patient 6 developed keratopathy in the fellow treated eye), or refused treatment for personal reasons (Patient 7).

Among MTX-treated eyes, a complete response was achieved in seven eyes (77.8%), of which six had stable vision and one experienced visual improvement after a mean (± standard deviation) of five (± three) injections (online supplementary Table 4). This outcome is comparable to a series from the United States (n=10), which reported a complete response rate of 80% and visual stability or improvement in 50% of cases following a mean of six MTX injections (range, 1-10).[16] Of the remaining two MTX-treated eyes, one showed progressive disease and one experienced ocular relapse. In Patient 6, the right eye initially improved after two injections, but further treatment was declined, resulting in worsening vitritis 3 months later. In Patient 5, the left eye initially presented with neovascular glaucoma. After 14 injections, a complete response was maintained for 6 months, followed by relapse 9 months later with anterior chamber infiltrate. Further injections were challenging due to PCNSL-related organic psychosis after three additional doses. Despite a similar number of injections, the ocular relapse rate in our study (11.1%) was lower than that reported in a series from the United States (40%) involving seven patients with an average of six MTX injections,[16] and was comparable to the largest Chinese cohort, where patients received an average of five injections (10%).[6] Keratopathy, the most common adverse effect of intravitreal MTX,[17,18] was mild in our series and resolved with preservative-free lubricants, bandage contact lenses, and oral folic acid. The incidence in our cohort (33%) was lower than the 100% reported in other studies.[4,18] This difference may be attributable to the lower number of MTX injections, as well as our practices of compressing the injection site with a cotton-tipped applicator, performing thorough saline rinses to minimise corneal exposure, and pre-emptively prescribing preservative-free lubricants.

TABLE. Treatment outcomes of patients with primary vitreoretinal lymphoma

Patient	Involved eye(s)	Brain biopsy	Chemo with or without WBRT	Ocular outcome*		Ocular outcome at final follow-up		Progression-free period, mo		CNS relapse	Treatment-related ocular complications
				R	L	R	L	R	L		
1	R	DLBCL	Chemo	Y^{V+M}	N/A	CR	N/A	2	N/A	Yes	N/A
2	BE	DLBCL	Chemo	Y^{V+M}	Y^{V+M}	CR	CR	66	82	No	N/A
3	L→R	DLBCL	Chemo + WBRT	Y^{V}	Y^{V}	CR	CR	10	32	No	Cataract
4	R	DLBCL	Chemo	Y^{V}	N/A	CR	N/A	15	N/A	Yes	N/A
5†	R→L	DLBCL	Chemo + WBRT	Y^{V}	Y^{V+M}	CR	CR	N/A	9	Yes	N/A
6	BE	DLBCL	Chemo + WBRT	Y^{M}	Y^{V}	PD	PD	3	N/A	Yes	PEE
7	L	DLBCL	Chemo + WBRT	N/A	Y^{V}	N/A	PD	N/A	N/A	Yes	N/A
8	R→L	N/A	N/A	Y^{V}	Y^{V}	CR	CR	29	5	N/A	N/A
9	L→R	N/A	N/A	Y^{M}	Y^{V+M}	CR	CR	48	50	N/A	Corneal filaments + PEE, cataract
10	R→L	N/A	N/A	Y^{V+M}	Y^{V+M}	CR	CR	8	1	N/A	PEE

Abbreviations: BE = both eyes; Chemo = chemotherapy; CNS = central nervous system; CR = complete response; DLBCL = diffuse large B-cell lymphoma; L = left; MTX = methotrexate; N/A = not applicable; PCNSL = primary central nervous system lymphoma; PD = progressive disease; PEE = punctate epithelial erosions; R = right; WBRT = whole-brain radiotherapy

* Y^{V} denotes eyes that received vitrectomy and declined intravitreal MTX; Y^{V+M} denotes eyes that received vitrectomy and intravitreal MTX; Y^{M} denotes eyes that received intravitreal MTX and declined vitrectomy

† Organic psychosis related to PCNSL precluded accurate visual acuity testing during the final follow-up period; the left eye achieved a CR for 6 months and then relapsed with hypopyon, which resolved after three further injections; the right eye showed a pale disc with diffuse atrophy

Therapeutic role of vitrectomy alone in primary vitreoretinal lymphoma

Although vitrectomy is pivotal for the diagnosis of PVRL, its therapeutic role remains controversial. The largest Chinese study (n=61) demonstrated complete clearance of malignant cells in 19.7% of cases after vitrectomy alone,[6] whereas the largest study in a Western population (n=150)[19] found no difference in outcomes between vitrectomised and non-vitrectomised eyes. In our study, eight eyes underwent vitrectomy alone without MTX. A complete response was observed in six of eight eyes (75%). One patient with isolated ocular PVRL (Patient 8) achieved a complete response and visual improvement (from 20/600 in the right eye and 20/70 in the left eye to 20/30 bilaterally) with vitrectomy alone; the patient did not receive intravitreal MTX (due to patient reluctance) or systemic chemotherapy with or without radiation therapy. This response was maintained at the latest follow-up, 29 months and 5 months after vitrectomy in the right and left eyes, respectively.

It is plausible that vitrectomy removed the vitreous scaffold necessary for lymphocyte proliferation and concurrently reduced the tumour burden.[19] This process may have enabled effective tumour control by the host immune system, a mechanism described in rare reports of spontaneous regression of PVRL.[20] Nevertheless, regular monitoring is recommended, and treatment should be initiated if any new chorioretinal infiltrates or vitreous opacities are detected. Given the favourable visual improvement observed in patients treated with vitrectomy alone (62.5%), therapeutic vitrectomy may be considered in those who are intolerant of, or unwilling to, undergo weekly MTX injections.

Conclusion and future directions

This study represents the first and largest series to date describing the diagnosis and treatment outcomes of PVRL in Hong Kong. To address the low positivity rate of cytological testing, there is a need for heightened clinical suspicion, greater awareness of sensitive adjunctive tests, and enhanced communication among ophthalmologists, oncologists, and cytopathologists to improve diagnostic accuracy in suspected PVRL cases or when initial results are equivocal. Despite the retrospective design and limited sample size, attributable to the rarity of PVRL, our findings align with emerging evidence suggesting that fewer intravitreal MTX injections or therapeutic vitrectomy alone, followed by observation, can be effective, particularly in patients who are frail or intolerant of intensive injection regimens. Future research should prioritise prospective randomised studies to identify optimal treatment strategies that preserve vision and quality of life in patients with PVRL.

Author contributions

Concept or design: ACY Mak.
Acquisition of data: ASH Chee.
Analysis or interpretation of data: ASH Chee.
Drafting of the manuscript: ASH Chee.
Critical revision of the manuscript for important intellectual content: ACY Mak, KW Kam, MSC Li, M Ho, ME Brelen, LJ Chen, WWK Yip, AL Young.

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

All authors have disclosed no conflict of interest.

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Supplementary material

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