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(Case Report)

Primary vitreoretinal high-grade B-cell lymphoma: A Case report and a brief review of the literature

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Abstract

Primary vitreoretinal lymphoma (PVRL) is a rare, aggressive form of non-Hodgkin lymphoma that primarily affects the retina and vitreous humor. Classified as a subset of primary central nervous system lymphoma (PCNSL), it usually manifests as a diffuse large B-cell lymphoma (DLBCL) and is notorious for mimicking chronic uveitis.

A 68-year-old immunocompetent female presented with a four-month history of blurred vision and mild photophobia, with fundoscopy showing vitreous haze, multifocal creamy-yellow subretinal infiltrates, and retinal pigment epithelium changes. She was originally treated for inflammatory uveitis with doxycycline and corticosteroids. The diagnosis of PVRL was confirmed by polymerase chain reaction (PCR) demonstrating IgH gene rearrangement and monoclonality, along with detection of the MYD88 L265P mutation. Treatment was methotrexate twice weekly for four weeks, followed by methotrexate weekly for eight weeks and monthly maintenance.

After 3 months, the haze had cleared, and the subretinal infiltration had resolved, with improvement in visual acuity. Eleven months later, a brain MRI showed a 2-cm enhancement lesion in the frontal lobe and multifocal periventricular nodules. She received high-dose methotrexate with rituximab followed by whole-brain radiotherapy. Six months later, the repeat MRI showed an increase in size of the left frontal lobe and several new subependymal and leptomeningeal enhancements. The patient was transitioned to palliative care with the goal of care to be comfort measures. The patient died 9 months later.

This case highlights the diagnostic challenges of primary vitreoretinal lymphoma and aims to increase awareness of this rare disease.

Keywords: Primary vitreoretinal lymphoma; Primary central nervous system lymphoma; Chronic uveitis; MYD88 L265P mutation; Diffuse large B-cell lymphoma; Diagnostic pars plana vitrectomy; Whole-brain radiotherapy

1. Introduction

Primary vitreoretinal lymphoma (PVRL) is a rare non-Hodgkin lymphoma that affects the vitreous, retina, or optic nerve. PVRL is confined to the intraocular compartment without brain involvement, making it a rare subgroup of PCNSL. Most cases of PVRL reported are high-grade diffuse large B-cell lymphoma (DLBCL). PVRL has a poor prognosis due to

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a high risk of CNS relapse. [1] The overall mortality of PVRL during follow-up between 12- and 35-months ranges from 9% to 81%. [2]

Diagnosis of PVRL is often delayed because of the masquerade as chronic uveitis. In most cases, patients are treated with corticosteroids for presumed uveitis and can achieve transient symptomatic improvement, which further delays the diagnosis. PVRL is a challenging diagnosis because it often presents with nonspecific ocular symptoms such as blurred vision, decreased visual acuity, and floaters. It is especially difficult to distinguish PVRL from chronic posterior segment uveitis. Even so, key features of PVRL include vitreous opacities, creamy lesions with yellow infiltrates, and "leopard-skin" infiltrates overlying the mass. [1,2]

Diagnostic vitrectomy is the gold standard for diagnosis. Cytological examination of lymphocytic cells in the eye is the most specific practice for definitive diagnosis of PVRL. Diagnosis also requires an IL-10/IL-6 ratio > 1 in the vitreous fluid, positive *IgH* gene rearrangement detected by polymerase chain reaction (PCR) and histologically confirmed DLBCL in the CNS or other systemic organs. [3]

Treatment of PVRL includes both local and systemic therapies. PVRLs are usually responsive to both radiotherapy and chemotherapy. The first line of treatment is high-dose systemic chemotherapy along with intravitreal chemotherapy and/or ocular radiotherapy. [1]

We report this case to highlight the diagnostic challenges of primary vitreoretinal lymphoma and its ability to mimic chronic uveitis. Diagnosis and treatment planning require a multidisciplinary team discussion to achieve early identification and guide optimal patient management.

2. Case Presentation

2.1. Clinical Presentation

A 68-year-old immunocompetent female presented with a 4-month history of progressive floaters, blurred vision, and mild photophobia in the left eye, followed by similar symptoms involving the right eye over the preceding 6 weeks. She had initially been treated by an optometrist with topical corticosteroids and oral doxycycline for presumed posterior uveitis, without clinical improvement. A trial of oral prednisone (40 mg daily for 3 weeks) transiently reduced floaters, but symptoms recurred upon tapering. She sought ophthalmic oncology consultation due to worsening visual acuity (20/100 OD, 20/200 OS) and new-onset "flashing lights." She denied headaches, focal weakness, or B-symptoms.

2.2. Physical Examination, Imaging, and Differential Diagnosis

Eye examination was reported as follows: Best-corrected visual acuity was reduced bilaterally. Slit-lamp examination revealed mild anterior chamber cells (1+) (evidence of mild inflammation in the anterior chamber). Funduscopy showed vitreous haze, multifocal creamy-yellow subretinal infiltrates, and retinal pigment epithelium alterations in both eyes: no iris nodules or hypopyon (accumulation of white blood cells that pools in the bottom of the eye's anterior chamber). Personal and family history were negative for lymphoma or autoimmune disease. Laboratory studies: normal LDH and ACE, and negative infectious workup (toxoplasmosis, syphilis, TB, CMV, HSV).

MRI of the brain and orbits with contrast showed mild vitreous enhancement but no intraocular mass or parenchymal lesions. Fluorescein angiography demonstrated hyperfluorescence and late leakage at subretinal lesion sites. Ocular B-scan ultrasonography revealed moderate vitreous opacities without retinal detachment. Differential diagnosis included viral retinitis, sarcoidosis, PVRL, and intermediate uveitis. Clinical and imaging findings favored PVRL over inflammatory etiologies given the lack of response to steroids and bilateral involvement.

2.3. Multidisciplinary Tumor Board Discussion

The tumor board included ophthalmology, neuro-oncology, hematopathology, and radiology. Discussion centered on: (1) the high suspicion for PVRL despite absence of support by the initial MRI; (2) the need for diagnostic vitrectomy rather than empiric steroids; (3) staging for systemic or CNS disease. The team agreed that further delay risked vision loss and CNS progression.

They debated diagnostic vitrectomy and chorioretinal biopsy; vitrectomy was chosen for lower morbidity. Key decision points: absence of B-symptoms or systemic lymphadenopathy made extraocular primary lymphoma less likely. The board recommended immediate diagnostic vitrectomy (undiluted sample) with flow cytometry, cytology, and cytokine

analysis. They also ordered a repeat contrast-enhanced brain MRI with diffusion-weighted imaging, plus lumbar puncture for CSF cytology and flow cytometry to rule out occult CNS involvement.

2.4. Special Studies, Pathology, IHC, and Molecular Studies

Diagnostic pars plana vitrectomy yielded vitreous fluid. Cytospin preparation showed large atypical lymphoid cells with irregular nuclear contours, prominent nucleoli, and scant cytoplasm. Immunohistochemistry (IHC) on cell block: CD45+, CD20+, PAX5+, BCL6+, MUM1+, CD10-, BCL2 (weak), MYC (40% of cells positive). The Ki-67 proliferation index was high at 85% nuclear staining. (**Figure 1 A, B, C**) Flow cytometry identified a clonal B-cell population with CD19+, CD20+, surface light chain restriction (kappa). Cytokine analysis: markedly elevated IL-10 (250 pg/mL) and IL-10/IL-6 ratio >1.0. Molecular studies: PCR for IgH gene rearrangement confirmed monoclonality. MYD88 L265P mutation was detected by allele-specific PCR. CSF analysis was negative for malignant cells and repeat brain MRI remained unremarkable.

Given comprehensive staging showing no evidence of systemic or primary CNS lymphoma, negative brain MRI and CSF studies, and the absence of B-symptoms, lymphadenopathy, or organomegaly, the diagnosis was PVRL, non-GCB subtype.

2.5. Treatment, Follow-Up, and Progression to Brain Lymphoma

The patient was treated with intravitreal methotrexate (400 μg/0.1 mL) twice weekly for 4 weeks as induction, then weekly for 8 weeks, followed by monthly maintenance. After 3 months, the vitreous haze had cleared, the subretinal infiltrates had resolved, and visual acuity improved to 20/40 in the right eye and 20/60 in the left. Systemic evaluation remained negative.

At 11 months post-diagnosis, she developed progressive short-term memory loss and unsteady gait. Brain MRI showed a 2 cm enhancing lesion in the left frontal lobe and multifocal periventricular nodules. CSF cytology and flow cytometry were positive for CD20+ clonal B cells with identical IgH rearrangement and MYD88 L265P mutation. Diagnosis was secondary CNS lymphoma. She received high-dose methotrexate (8 g/m^2) with rituximab, followed by whole-brain radiotherapy (24 Gy). Six months after completing whole-brain radiotherapy (WBRT), having achieved a partial response initially, the patient presented with worsening confusion, word-finding difficulty, and a new-onset generalized seizure. Performance status declined from ECOG 1 to 3 over 3–4 weeks.

Repeat brain MRI with contrast revealed interval increase in size of the left frontal lesion (now 3.2 cm with rim enhancement) and several new subependymal and leptomeningeal enhancing nodules. CSF analysis showed persistent CD20+ clonal B cells, now with high MYC expression and loss of BCL6 by flow cytometry, suggesting clonal evolution. Repeat PET/CT remained negative for systemic disease.

Tumor board discussion convened again, and options considered included: high-dose cytarabine-based chemotherapy (if renal function is adequate), Ibrutinib-based regimens (BTK inhibitor, given blood-brain barrier penetration), pemetrexed or topotecan as salvage, and best supportive care given declining performance status. The patient was transitioned to palliative-intent ibrutinib monotherapy but developed progressive cognitive decline and aspiration pneumonia. A goals-of-care discussion with family led to comfort measures. The patient died 9 months after CNS progression (21 months from initial ocular diagnosis).

The family requested an autopsy, and the findings confirmed isolated CNS and ocular lymphoma with no systemic involvement, reinforcing the primary CNS lymphoma spectrum.

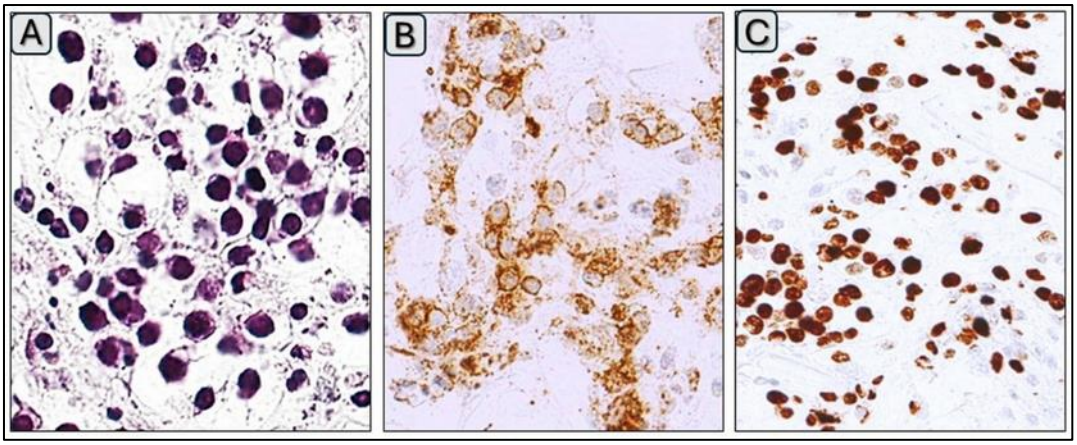

Figure 1 Microscopic and immunohistochemical features of vitreoretinal high-grade B-cell lymphoma

- 1A**:** High-power view showing large atypical lymphoid cells with irregular nuclear contours, prominent nucleoli, and scant cytoplasm (H&E X20, cytology cytospin)
- 1B**:** Tumor lymphoid cells positive for CD20
- 1C**:** Tumor lymphoid cells with high proliferation index (> 85% Ki-67 nuclear staining)

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

Primary vitreoretinal lymphoma (PVRL), a subset of primary central nervous system lymphoma (PCNSL), is an extremely rare ocular tumor. It is considered a variant or initial manifestation of PCNSL even when the CNS is uninvolved at diagnosis. The term "primary" distinguishes it from secondary ocular involvement (e.g., from systemic diffuse large B-cell lymphoma or other lymphomas). PVRL was first described in 1951. Primary ocular lymphomas can be divided into 2 groups: those that begin in the uvea (Primary Uveal Lymphoma) and those that begin in either the vitreous or the retina (PVRL). [2,4]

PVRL is considered a subtype of primary central nervous system lymphoma (PCNSL), a rare form of non-Hodgkin lymphoma in which 95% of cases are DLBCL [4]; however, few cases of a T-cell variant have been reported. [2] This is distinct from secondary lymphomas in the setting of systemic disease because PVRL is often mistaken for infectious or inflammatory conditions, and patients often present with CNS involvement due to delayed diagnosis.

The age-adjusted incidence of PVRL is approximately 0.23 cases per million. [4] About 65% to 90% of patients with Primary Vitreoretinal Lymphoma (PVRL) will eventually develop Central Nervous System (CNS) lymphoma. [5] There are only a few documented risk factors for PVRL. Age is a major risk factor, with a median age of over 63 years and 20% of patients aged 80 or older. HIV and EBV are other risk factors for PVRL. [4]

3.2. Pathogenesis, Pathophysiology

The molecular pathogenesis of PVRL has only become clear within the last decade. Although immunosuppression was previously hypothesized to be a major factor, mutations within the activated B-cell (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) [Also referred to as non-GCB subtype] are now recognized as key drivers of PVRL development. [6,7] The most common alterations include allelic mutations in myeloid differentiation factor 88 (MYD88) and the B-cell co-receptor, CD79B. [4,8] According to Bonzheim et al., MYD88, which is an adaptor protein within the toll-like receptor pathway, is mutated in 70% of DLBCLs, from which most PVRL cases arise. The MYD88 L265P mutation is commonly identified in PVRL and other lymphomas occurring within immune-privileged sites. The MYD88 and CD79B mutations promote constitutive NF-ϰβ signaling, resulting in consistent proliferation and survival of malignant lymphocytes within ocular tissues. [6,7]

Infiltration of vitreous and retinal tissue by malignant B-lymphocytes characterizes the pathophysiology of PVRL. Cytokines and chemokines facilitate lymphocyte localization to the retinal pigment epithelium (RPE), where a lack of immune surveillance in this immune-privileged site may further promote tumor cell survival. Elevated levels of interleukin-10 (IL-10), a major anti-inflammatory and immunosuppressive protein, are characteristic of PVRL.

Additionally, chemokine pathways involving CXCR4 and CXCR5 are associated with the migration of malignant B-lymphocytes to ocular tissues. The recognition of these biomarkers has enhanced diagnostic yield and modernized PVRL detection. [7,8]

3.3. Comparative Analysis of Our Case with Existing Literature

PVRL is a rare intraocular malignancy that poses a formidable diagnostic challenge, frequently masquerading as chronic posterior uveitis. [1] In our patient, the 4-month delay in diagnosis, initial misattribution to an inflammatory etiology, and transient partial response to systemic corticosteroids mirror the classic clinical course described in the literature. [9]

A review of large case series indicates that the median time from symptom onset to PVRL diagnosis ranges from 6 to 40 months, largely due to the indiscriminate use of corticosteroids, which lyse the fragile lymphoma cells and obscure cytological evaluation. [1,4]

Consistent with established reports, our patient presented with bilateral involvement, marked vitreous haze, and characteristic subretinal infiltrates. The definitive diagnosis was established by diagnostic pars plana vitrectomy, which remains the gold standard, and was further supported by detection of the MYD88 L265P mutation and an elevated IL-10/IL-6 ratio. [10,11] The MYD88 L265P mutation is present in approximately 69% to 80% of PVRL cases and serves as a critical diagnostic adjunct, particularly when cytomorphology is equivocal. [11]

4. What Have We Learned from This Case?

What we have learned from this case reinforces several critical clinical insights. First, the presence of bilateral, steroid-refractory posterior uveitis in an elderly patient must raise a high index of suspicion for PVRL, prompting early consideration of diagnostic vitrectomy rather than prolonged empiric immunosuppression.

Second, while our patient achieved an excellent initial ocular response to intravitreal methotrexate, the subsequent progression to secondary central nervous system (CNS) lymphoma at 11 months underscores the aggressive natural history of the disease. Literature suggests that up to 58% to 92% of PVRL patients eventually develop CNS involvement, which remains the primary driver of mortality. [4,12] The clonal evolution observed in our patient's cerebrospinal fluid, characterized by high MYC expression and loss of BCL6, highlights the dynamic biological nature of the tumor and the necessity for rigorous, long-term CNS surveillance even after ocular remission.

This case challenges the reliance on localized therapy alone for PVRL, emphasizing the need for multidisciplinary management and the exploration of novel systemic and targeted therapies to mitigate the high risk of CNS relapse.

Abbreviations

- Primary vitreoretinal lymphoma (PVRL)
- Primary central nervous system lymphoma (PCNSL)
- Diffuse large B-cell lymphoma (DLBCL)
- Immunohistochemistry (IHC)
- Whole-brain radiotherapy (WBRT)

5. Conclusion

This case of primary vitreoretinal high-grade B-cell lymphoma illustrates the critical diagnostic challenges and aggressive clinical trajectory inherent to this rare malignancy. We present this case to underscore the imperative of recognizing steroid-refractory uveitis as a potential masquerade syndrome, where timely diagnostic vitrectomy and advanced molecular testing, such as MYD88 L265P mutation analysis, are paramount.

Furthermore, this report highlights the high propensity for devastating central nervous system progression despite successful local ocular control. By documenting the clonal evolution associated with CNS relapses, this case adds valuable insight into the complex tumor biology of PVRL. It underscores the medical community that multidisciplinary collaboration and vigilant neuro-oncological surveillance are essential, and it advocates for continued research into systemic prophylactic strategies to improve the ultimately poor prognosis of these patients.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

- Payment/services information: All authors have declared that they received no financial support from any organization for the submitted work.
- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

This work did not involve any studies on human or animal subjects performed by the authors. It was a retrospective review of archival pathology material collected during routine clinical care, and all data were fully de-identified before analysis.

Statement of informed consent

The patient expired; informed consent for the publication of this case was obtained from the patient's family.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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