**Abstract**

Primary vitreoretinal lymphoma (PVRL) is the most common intraocular lymphoma occurring in the eye. It is a high-grade typically B-cell malignancy, arising in the retina, and is often associated with central nervous system (CNS) disease and thereby a poor prognosis. It needs to be distinguished from choroidal low-grade B-cell lymphomas, which do not disseminate to the brain and have a good prognosis. Because of the rarity of PVRL, information is lacking regarding its true incidence, its geographical or ethnic variation, and underlying risk factors apart from immunosuppression associated with human immunodeficiency virus (HIV) and Epstein Barr virus. PVRL often presents masquerading as other intraocular diseases and is therefore often associated with diagnostic delays. This is compounded by the fragility of the neoplastic B cells, which hampers vitrectomy yields and pathological work-up. The latter includes cytomorphology and immunoprofiling, with adjunctive tests such as cytokine analysis, polymerase chain reaction for clonality, *MYD88* mutational testing, and possibly bespoke next generation sequencing. Recent examinations of PVRL and CNSL using whole genome sequencing confirm that these tumors arise from activated postgerminal center cells, reflecting their aggressive course in most cases. The treatment of PVRL varies between centers and is dependent on presence or absence of concomitant CNS disease. The prognosis remains poor, and yet progress is steadily being made through international collaborative clinical trials.

**Introduction**

Intraocular lymphomas arise in different parts of the eye but can be essentially subdivided into 2 groups: a) those that arise in the vitreoretina and b) those that occur in the uvea.1

Although the lymphomas arising in the vitreous and/or retina are usually primary tumors, often in association with central nervous system (CNS) disease, uveal lymphomas can be further subdivided into those that arise as a primary disease or as a secondary manifestation of systemic non-Hodgkin lymphoma (NHL).1,2 This review will concentrate on primary vitreoretinal lymphomas (PVRL) only: the reader is referred to other reviews on the topic of primary and secondary lymphomas of the uvea, as they will not be covered herein.1,3‒5

Primary vitreoretinal lymphoma is a rare disease but by far the most common intraocular lymphoma, with an estimated incidence of 0.46 per 100,000 person years.5,6 The true incidence of PVRL is unknown because as yet there is no central registry for this rare disease. Primary vitreoretinal lymphoma is an aggressive high-grade NHL, which is closely related to primary CNS lymphoma (PCNSL). Most PVRL are large B-cell lymphomas, according to the World Health Organization’s lymphoma classification,7 with only exceptionally rare cases of primary T-cell VRL having been described.8 At present PVRL is associated with a poor prognosis9,10 due to delays in diagnosis and lack of effective therapies. The clinical and pathological features of PVRL are outlined in separate sections below, followed by a brief overview of current PVRL treatment.

**Clinical Features, Assessment, and Diagnostic Evaluation of PVRL**

Primary vitreoretinal lymphoma most often affects patients over the age of 50 years, with a mean age of 63, with no gender prevalence.2,10 Rarely, however, PVRL are seen in younger individuals, particularly those who are immunocompromised as a result of treatment or due to human immunodeficiency virus (HIV). Inexplicably, the incidence of PVRL has been shown to be increasing, even in patients without any forms of immunosuppression. Although the most important risk factors for PVRL/PCNSL are HIV and Epstein Barr virus infection status,11 there are no other known risk factors for PVRL. Due to the rarity of the disease, systematic studies investigating any possible geographical or racial variation of PVRL have not been undertaken to date. The authors are aiming to address this through future efforts to establish an international multicenter PVRL database.

An insidious onset associated with delays in diagnosis of PVRL is common.2,5,9 The mean duration of PVRL symptoms before diagnosis is 6 months, but in some cases, symptoms precede diagnosis by 2–3 years before lymphoma is even suspected. Studies have reported a wide range of nonspecific symptoms for PVRL patients, including blurred vision in 40–50% of cases, decreased visual acuity in 25–30%, and floaters in 20–25%.1,2

The clinical signs of PVRL vary significantly between patients and can mimic a wide range of other ocular diseases; hence, PVRL has often been termed as a masquerade syndrome. The signs are bilateral in about 60–90% of patients but are often asymmetrical at presentation, appearing clinically as unilateral involvement due to the uneven distribution of disease.1,2

Lymphomatous deposits may initially accumulate around the retinal blood vessels and can be visible on ophthalmoscopy as perivascular sheathing, and therefore mimic vasculitis (Fig. 1). Multiple cream-colored deposits can also develop with time, resembling drusen or “white-dot” syndrome. These may also result in punched-out or atrophic retinal pigment epithelial (RPE) lesions. Over the course of the disease, the lymphomatous infiltrations coalesce and become more extensive, eventually replacing the entire thickness of the retina, resulting in it becoming opaque in the affected areas (Fig. 1).

The tumor cells are able to permeate between the RPE, accumulating in large deposits on the inner side of the Bruch membrane under the RPE in the so-called “subretinal space.” The Bruch membrane, however, seems to be impenetrable for the lymphoma cells, as PVRL very rarely extends into the choroid. The lymphoma cells closest to the choriocapillaris and the retinal vessels tend to remain viable, whereas those more distant from the blood source become necrotic and undergo apoptosis.

Primary vitreoretinal lymphoma formation near the macula may resemble a disciform scar. Optic nerve infiltration causes disc swelling and must be distinguished from papilledema caused by raised intracranial hypertension secondary to intracranial disease.12

Fluorescein angiography shows a variety of features, such as staining of the above-mentioned subretinal deposits, RPE window defects (leading to “leopard skin” appearance) (Figs. 1B, D), diffuse RPE mottling or stippling, and rarely, vascular leakage and macular edema.13

Primary vitreoretinal lymphoma cells can percolate up into the vitreous cavity and form visible clumps or aggregates within a hazy vitreous, causing difficulties for investigation on fundoscopy. These neoplastic cells within the vitreous may encircle the lens and extend into the anterior chamber, resulting in aqueous cells, flare, and keratic precipitates on slit-lamp microscopy.14 Cellular aggregates may also form on the iris causing heterochromia and also within the trabecular meshwork, resulting in secondary angle closure.1,2

Several secondary effects can develop in the eye as a result of PVRL involvement. For example, the retinal vasculopathy described above can cause exudation, macular edema, and serous retinal detachment. Vascular occlusions may result in irregular retinal infarcts and hemorrhages, which can in turn resemble acute retinal necrosis and various forms of retinitis.15,16 Iris neovascularization may develop, resulting in secondary glaucoma, hyphema, and painful, red eye. These appearances can be mistaken for uveitis and neovascular glaucoma; hence, PVRL is a “chameleon” presenting under the camouflage of other diseases and must always be considered in the differential diagnosis.1

*PVRL and Concurrent CNSL*

Lymphomatous involvement of the CNS can be concomitant to PVRL, precede it, or be antecedent to it. Further, CNSL may be focal and/or diffuse. Most CNSL occur in the frontal lobes, typically causing behavioral changes. Other focal neurologic signs include hemiparesis in 40–50% and cerebellar signs (including ataxia) in 15–40%. Diffuse leptomeningeal involvement is common in PCNSL and causes a wide variety of sensory and motor deficits. Cerebrospinal fluid (CSF) dissemination is detected during staging work-up in only 10–15% of cases.10 For these reasons, PVRL should be considered in any patient with uveitis and neurological symptoms.

**Biological Features of PVRL**

The majority (~95%) of PVRL can be classified as diffuse large B-cell lymphoma (DLBCL); however, due to unique clinical and biological features, PVRL (and associated PNCSL) is recognized as a specific subtype of lymphoma in the World Health Organization’s lymphoma classification.7

The bulk of evidence in the literature suggests that PVRL belongs to the activated B-cell (ABC) subtype of DLBCL, according to its immunoprofile profile and mutational status, in 80–90% of cases.17 In addition to the pan‒B-cell markers (ie, CD20, PAX5, and CD79a), PVRL expresses MUM1/IRF4, commonly BCL6 and BCL2, and usually lacks CD10 and plasma cell markers (eg, Vs38c, CD138).18 This immunoprofile suggests that PVRL are derived from cells at a late stage in the germinal center B-cell differentiation.18‒20

Primary vitreoretinal lymphomas monotypically express immunoglobulin heavy chains (either IgM or both IgM and IgD) and light chains.18 The cellular proliferation and apoptotic rates are very high, also reflected in the lytic cellular background often seen in vitrectomy specimens. Primary vitreoretinal lymphomas commonly demonstrate a high number of somatic hypermutations (SHM) of the rearranged immunoglobulin genes in most cases but without evidence for so-called ongoing hypermutations. Somatic hypermutation is the process by which mutations are introduced into the rearranged immunoglobulin genes of germinal center B cells to increase the binding affinity of the B-cell receptor. Similar to PCNSL, PVRL frequently exhibits immunoglobulin rearrangements with restricted usage of IGHV4-34.18,21,22

Due to their rarity and also the fragility of the tumor cells, genetic studies of PVRL are sparse; hence, data has been extrapolated from investigations conducted on PCNSL. Earlier studies of PVRL using polymerase chain reaction (PCR) have demonstrated a high frequency of IGH/BCL2 rearrangements as a result of the t(14;18) translocation, which occur in 85‒90% of follicular lymphoma and in about 30% of DLBCL of germinal center B-cell type.23,24 These results, however, are somewhat in contrast to the evidence that most PVRL are of ABC type, which typically lack *BCL2* rearrangements, and also with the fact that BCL2 translocations are rare in PCNSL.25 This may reflect a subset of PVRL of a less aggressive nature, and the clinical courses of some patients do indeed demonstrate this (Nathalie Cassoux, personal communication).

Translocations involving the *BCL6* oncogene occur in 17‒47% of PCNSL, and activation of this master regulator of the germinal center reaction may be partly responsible for the arrest in the terminal B-cell differentiation stage in PCNSL and PVRL.25,26 The presence of *BCL6* translocations has not been investigated in PVRL as yet.

Using a high-resolution single nucleotide polymorphism (SNP) array for the identification of copy number variations, alterations with common gains on chromosomes 1q, 18q, and 19q and frequent losses on 6q (alterations that are also frequently identified in PCNSL) have been demonstrated in PVRL.27

Recently, several studies using conventional techniques (eg, Sanger or next generation sequencing) have analyzed the mutational landscape of PCNSL and identified high frequencies of a) mutations in *MYD88*, the gene encoding myeloid differentiation factor 88 (*MYD88*), a member of the toll-like receptor pathway; b) members of the B-cell receptor signaling pathway, including *CD79B*; and c) other genes resulting in a constitutive activation of *NF-KB* signaling.28‒33

Furthermore, data generated by whole exome sequencing in PCNSL suggest a major impact of aberrant SHM on the mutational profile of PCNSL. In addition to well-known targets, such as *MYC*, *PAX5,* and *PIM1*, aberrant SHM seems to target additional genes in PCNSL, some of which are involved in CNS development.34

Interestingly, there are mutations affecting *MYD88* (usually the canonical L265P mutation) and *CD79B* that seem to be enriched specifically in DLBCL of immune-privileged sites (ie, the testis and the CNS). For example, *MYD88* mutations have been found in 35–79% of PCNSL28,29,31,33,35,36 and were recently identified in ~70% of PVRL with or without concomitant cerebral involvement.30

Only a few studies examining epigenetic alterations and micro-RNA (miRNA) expression profiles in PVRL exist. Using a real-time PCR-based miRNA panel, Tuo et al37 compared miRNA expression profiles in vitreous aspirates of PVRL and uveitis and identified miR155 as consistently downregulated in PVRL specimens. The authors proposed miR155 as a potential novel biomarker in PVRL.37 However, Kakkassery et al38 used a targeted approach in assessing particular miRNA concentrations in the vitreous to differentiate between PVRL and inflammation based on previous studies on CSF in PCNSL patients.38 Baraniskin et al39,40 demonstrated an upregulation of miR-92, miR-19b, and miR-21 in the CSF of PCNSL patients, compared with CSF of patients with other neoplastic and inflammatory CNS diseases.39,40 Kakkassery and co-workers38 examined the same 3 miRNAs and demonstrated that this panel had respectable and reproducible sensitivity and specificity for diagnosing PVRL.38 Although further validation studies are required to confirm the value of this miRNA panel in PVRL diagnosis, these results are indeed promising, as it would assess the noncellular component of vitrectomy samples, leaving the often fragile cellular component for morphological and immunoprofiling analyses.

**Pathological Diagnosis of PVRL**

The standard surgical approach to diagnose or exclude PVRL is vitrectomy. If this approach does not render an unequivocal diagnosis, subretinal aspirate or chorioretinal biopsy can be performed either simultaneously or subsequently.41 For a detailed review of the surgical procedures, the reader is referred to the ophthalmological literature.5,42 The aspirated material can be used for cytological examination, immunocytochemistry, flow cytometry, molecular examinations, and determination of cytokine levels. Therefore, an efficient triage system needs to be in place to maximize the use of the limited material for the different techniques in the pathology laboratory, which ideally should be experienced in handling these samples. Communication between the clinical and laboratory teams is paramount to success.

Cytological material should either be used within an hour after aspiration, or alternatively put into culture medium or a mild fixative solution, such as HOPE (Hepes-glutamic acid buffer-mediated organic solvent protection effect) solution, which preserves cytological detail along with immunoreactivity and nucleic acids.43 An alternative fixative is Cytolyt.41 Cytological specimens are usually prepared with the cytospin technique onto slides, with the morphological stain being May-Grunewald-Giemsa (MGG) (Fig. 2) and 2‒3 unstained cytospins prepared from immunocytology. Alternatively, the cell-block technique with embedding in either paraffin or agar can be employed for cell-rich specimens (Fig. 2).44

The MGG-stained cytospins reveal the presence of medium-to-large, atypical lymphoid cells with increased nuclear/cytoplasmic ratio, basophilic cytoplasm, and irregular nuclei with 1 to several nucleoli in cases of PVRL (Fig. 2). However, in the background can be numerous reactive lymphocytes, macrophages, and lytic cells, which may complicate the interpretation of the immunostaining. Poor preservation of cytological detail may occur as a result of antecedent steroid therapy, which causes cell membrane rupture. Furthermore, it must be noted that atypical monocytes may also occur in reactive conditions, such as acute viral infection, and hence a CD68 stain should be included with T-cell markers (eg, CD2 or CD3) and B-cell markers (CD79a, CD20, or PAX5) in the initial work-up (Fig. 2). It should be noted that the advantage of the PAX5 stain is that it is nuclear and may highlight neoplastic B cells that have ruptured and no longer possess a distinct membrane for the CD20 stain.

The reported rates of sensitivity and specificity of cytology for the diagnosis of PVRL vary widely, but cytology alone is able to confirm PVRL in 45–60% of cases, and false positive results are considered rare.45‒47 Experienced technicians and ocular cytopathologists play a major role in this success rate.

As an alternative to immunohistochemistry or immunocytology, multicolor flow cytometry has been successfully employed for phenotyping of vitreous aspirates, with a reported sensitivity of 82% and 100% specificity.48 Monotypical expression can be demonstrated using the immunoglobulin light chains. Furthermore, T-cell subset ratios can usually be clearly defined using multiple gating. However, poor cellular preservation and abundant reactive T cells may limit the diagnostic yield and thereby the ability to make unequivocal statements.49

Molecular examination of vitreous specimens has become a valuable tool to confirm the morphological and immunocytological diagnosis of lymphoma. Identification of clonal immunoglobulin gene rearrangements using consensus primer sets, such as those developed by the BIOMED-2 consortium, is a mainstay in PVRL diagnosis.50 The sensitivity of clonality studies ranges between 65% and 95%, depending on the choice of primer sets, quality of material, and experience of the laboratory.41,46,51‒54

False negative results may still occur in PVRL, due to the large number of somatic mutations in the neoplastic PVRL B cells impeding primer binding in the variable region of the immunoglobulin gene. On the other hand, false positive results may occur, particularly in paucicellular samples, due to amplification of small populations of oligoclonal B lymphocytes.30,36 To avoid misdiagnosis of minor clonal expansions as evidence for lymphoma, all tests should be run in duplicate to confirm the presence of a dominant clone, and results should be interpreted with caution and only in the context of clinical and morphological findings. Determination of clonality is especially valuable for cases in which suspected intraocular dissemination or relapse of PCNSL or systemic lymphoma can be confirmed by proving or disproving a clonal relationship.

To further improve the application of molecular diagnostics in PVRL, Bonzheim et al30 made use of the common occurrence of *MYD88* mutations in PCNSL, identifying the canonical L265P mutation in ~70% of cases.30 Some centers are now using *MYD88* mutational analysis as an alternative to IgH-PCR in the diagnosis of PVRL, particularly in cases where the DNA yield is low. However, care must be taken in PVRL cases where the *MYD88* mutation is not present: this does not necessarily exclude lymphoma if the other findings still strongly support it.

Very recently, next generation sequencing studies (NGS) by Cani et al55 of 3 PVRL samples demonstrated *MYD88* gain-of-function mutations and loss of *CDKN2A*.55 Further, a focal loss of *AKT1* was observed in 1 case, and low level gain of chromosome 19 was observed in another (the targeted genes included *STK1, MLL4/KMT2D*, and *ARHGAP43*). These findings suggest that a NGS-targeted panel could be designed for PVRL as an adjunctive tool to the morphological and immunoprofiling studies, particularly in cases where there is minimal material.56

Some centers advocate the use of measurement of cytokine levels within ocular fluids (ie, aqueous humor and the vitreous) to provide adjunctive diagnostic evidence to cytology for the presence/absence of PVRL.2,53,57‒62 In particular, these centers measure the levels of interleukin (IL) 10 and IL6 and then compare their ratio: a high level of IL10 in pure vitreous or aqueous humor samples, or an IL10:IL6 ratio greater than 1 in diluted or undiluted samples, is considered evidence for PVRL. The techniques used to measure the IL10 and IL6 levels include enzyme-linked immunosorbent assay (ELISA) and multiplex-based cytometric bead array. The exact cut-off for the IL10 concentration or IL10:IL6 ratio may vary between laboratories, mainly due to differences in the methods applied, the conditions of sample harvesting and storage, techniques, and manufacturers of equipment and supplies, along with the dilution (known or unknown) of the vitreous samples and the laboratory’s own experience. Interleukin levels within intraocular fluids have also been proposed and used with some success to monitor response of PVRL under therapy.59,61,62 In larger series, the sensitivity of IL10 measurements and/or the IL10:IL6 ratio in PVRL is 80–90%, with virtually no false positives reported, making cytokine determination an additional valuable diagnostic tool.

**Management of PVRL**

As yet, international consensus guidelines for PVRL treatment have not been established, as the management remains quite controversial. The ultimate goal of treatment is to eradicate the PVRL cells, eliminating the potential reservoir of untreated disease within the eye that could cause recurrence or CNS infiltration. However, both the blood-brain and the blood-retinal barriers are important considerations for drug penetrance. It is clear that treatment of PCNSL/PVRL requires a multidisciplinary approach and that each patient’s case should be discussed in detail before treatment commences.63‒65 Orbital and ocular radiotherapy, intravitreal methotrexate and/or rituximab, high-dose systemic methotrexate (HD-MTX), myelo-ablative chemotherapy, and immunotherapy have been reported to achieve remission of PVRL, although many patients relapse with the recurrent disease occurring either in the form of ocular disease (even in the contralateral eye) or CNS lymphoma.9 The timing of the administration of whole brain radiotherapy (WBRT), either as CNS prophylaxis or for consolidation of existent disease, remains unclear. When HD-MTX is given with WBRT for consolidation, delayed neurotoxicity, particularly dementia, can be an important complication. Studies have suggested that WBRT may be deferred until relapse without compromising survival, and deferring WBRT may be the best approach in elderly patients. Alternatives to HD-MTX include dose-reduced WBRT and consolidative high-dose cytarabine (HD-Ara-C); high-dose chemotherapy and autologous stem cell transplantation for selected patients; and pomalidomide or ibrutinib, in conjunction with local therapy. The reader is referred to recent reviews on PVRL treatment, which understandably overlap with CNSL management.9,63,64,66,67

With a 5-year overall survival rate of less than 25%, the prognosis of PVRL remains poor despite advances in new treatments. In a study involving 16 centers from 7 countries from 1977 through 2005, Grimm et al65 reported a median progression-free survival and overall survival of 18 and 31 months, respectively, with a total mortality of 67.9% (150 of 221).65

**Summary**

Although PVRL is still a difficult disease to diagnose and treat, new advances have been made both in diagnostic imaging and molecular techniques, improving the detection of this highly aggressive disease. Further, with the advent of new targeted therapies for both PVRL and PCNSL, there is hope that if PVRL is detected sufficiently early, the prognoses will improve. Multicenter efforts are essential to improve data collection (eg, epidemiological and geographical information across the globe) to have a better understanding of the pathogenesis and biology of this disease. As current PVRL animal models are deficient in representing the course of this disease, coordinated biobanking of PVRL (and PNCSL) material surplus to diagnostics would allow for the identification of new drug targets.

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**FIGURE LEGENDS**

**Figure 1:**

Fundoscopy (A) and accompanying fluorescein angiogram (FA) (B) of the left eye of a 54-year-old female with scattered dot-like cream yellow deposits in the retina. Fundoscopy (C) and accompanying FA (D) of the same patient 2 months later with confluence of the yellow subretinal deposits and perivascular infiltrate mimicking vasculitis.

**Figure 2:**

A, Cytospin of a vitrectomy sample stained with MGG demonstrating medium to large pleomorphic cells with varying basophilic cytoplasm and dense nuclear chromatin (x60 magnification). B, Immunocytochemical staining of the same vitrectomy sample with clear positivity for the B-cell marker CD20 [alkaline phosphatase antialkaline phosphatase (APAAP), x60 magnification]. C, Cell-rich vitrectomy sample embedded in a paraffin cell block stained with hematoxylin and eosin with numerous medium-sized atypical lymphocytes with scattered blasts and macrophages (x40 magnification). D, Immunohistochemical staining of the same sample from C with the B-cell marker CD79a, highlighting the neoplastic B lymphocytes (APAAP, x20 magnification).