

# Primary vitreoretinal lymphoma: prevalence, impact, and management challenges

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**Abstract:** Primary vitreoretinal lymphoma (PVRL) is a rare and potentially fatal intraocular malignancy. More than half of PVRL cases eventually involve the central nervous system (CNS). PVRL frequently masquerades as chronic uveitis. Advanced imaging tests, such as optical coherence tomography and fundus autofluorescence, have been applied in the diagnosis of PVRL. Histology and immunohistochemistry, in combination with molecular tests and IL-10 analysis, have been demonstrated as reliable in diagnosing PVRL. Mortality is high in patients with PVRL associated with CNS involvement, and relapses are common. The use of systemic chemotherapy in addition to the local therapies has proved to extend the mean survival time of these patients. Local therapies, including intravitreal injections of methotrexate and/or rituximab and low-dose radiotherapy to the eye, have been shown to be extremely effective in controlling intraocular lymphoma.

**Keywords:** CNS lymphoma, malignancy, ocular tumor, treatment, investigations, prognosis

## Introduction

Primary intraocular lymphoma (PIOL), previously known as ocular reticulum cell sarcoma, was first described by Cooper and Riker<sup>1</sup> in 1951, followed by Givner<sup>2</sup> in 1955, as a malignant lymphoma of the uveal tract. Lymphomatous proliferations seen in the eye can essentially be subdivided into two groups: 1) those which occur in the vitreous and/or retina and 2) those which occur in the uvea.<sup>3</sup> Vitreoretinal lymphomas are lymphomas that arise primarily in the vitreous and/or retina and are considered as a part of the primary central nervous system lymphoma (PCNSL). Uveal lymphomas can be further divided into those which start as a primary disease in the uveal tract or those which occur as an ocular manifestation of systemic non-Hodgkin lymphoma.<sup>3,4</sup> In this review, we will concentrate on primary vitreoretinal lymphoma (PVRL) only. PVRL is a subset of PCNSL, where the lymphocytic neoplastic cells primarily affect the retina with or without involving the vitreous or the optic nerve and may not have brain or cerebrospinal fluid (CSF) involvement at presentation.<sup>4-6</sup> PVRL is a rare but potentially fatal intraocular malignancy. Ocular manifestations of PCNSL can occur or ultimately develop in approximately a quarter of patients with PCNSL.<sup>7,8</sup> With an increase in the incidence of PCNSL in recent times, there has been a similar increase in PVRL incidence worldwide.<sup>8,9</sup> PVRLs are usually diffuse large B-cell lymphomas with very few cases of primary T-cell VRL being described in the literature.<sup>10,11</sup> Presently, PVRL is associated with a poor prognosis, mainly due to delays in diagnosis and lack of effective therapies.<sup>12,13</sup> Systemic chemotherapy, along with ocular chemotherapy/radiation, forms the basis of treatment in PVRL. Many papers have been published recently, highlighting the clinical features, diagnosis, and treatment

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modalities available in PVRL.<sup>14–16</sup> With increase in PVRL cases due to better understanding and diagnosis of the disease, it is important to keep the readers updated of the varying clinical features and newer treatment options available. With this review article, we intend to discuss the clinical and pathological features of PVRL followed by an overview of current diagnostic and treatment options, prognosis, and also highlight the areas where further research can be considered in the management of PVRL.

## Demographic profile

PVRL, a rare intraocular malignancy, is a subset of PCNSL. It is a rare disease, with an approximate incidence of 0.047 cases per 100,000 people per year.<sup>17</sup> This represents 4%–6% of all brain tumors and less than 1% of all non-Hodgkin's lymphomas.<sup>9,18</sup> Fifteen percent of all PCNSL patients have intraocular disease, whereas over 50% of patients with PVRL develop CNS disease.<sup>19</sup> PVRL usually affects the adults in the fifth–sixth decades of life.<sup>20–22</sup> A few cases of PVRL seen during early childhood and adolescence have also been documented in the literature,<sup>23,24</sup> particularly in those who are immunocompromised as a result of treatment or due to HIV.

There seems to be no sex or racial predilection to the disease. However, a few reports suggest women to be more commonly affected than men, by 2:1 or even greater.<sup>21,25–28</sup>

## Etiopathogenesis

The etiology of PIOL/PCNSL is not very clear. Two theories have been implicated in the etiology of PVRL, namely 1) infectious theory and 2) hematological spread. Infections with Epstein–Barr virus or HIV virus, especially in immunocompromised patients, attracts the lymphoid cells while the neoplastic transformation to lymphoid malignancy takes place later, at the eye and/or CNS. This is supported by the finding that Epstein–Barr virus is invariably found in AIDS patients with PCNSL and usually runs a more aggressive clinical course.<sup>29</sup> *Toxoplasma gondii* has also been found in B-cell lymphoma cells in two out of ten PIOL samples, leading to speculation on the possible role of this organism in the etiology of PVRL.<sup>30</sup> Another theory is the hematological spread of neoplastic cells from nodal and extranodal sites to ocular and CNS structures.<sup>26</sup> According to this theory, B-cell chemokines may selectively attract the lymphoma cells from the choroidal circulation to the retinal pigment epithelium (RPE) and/or retina. B-cell chemokine receptors CXCR4 and CXCR5 were detected in the lymphoma cells, whereas the ligands BLC and SDF-1 were detected only in the RPE, thus supporting this vascular theory.<sup>31</sup>

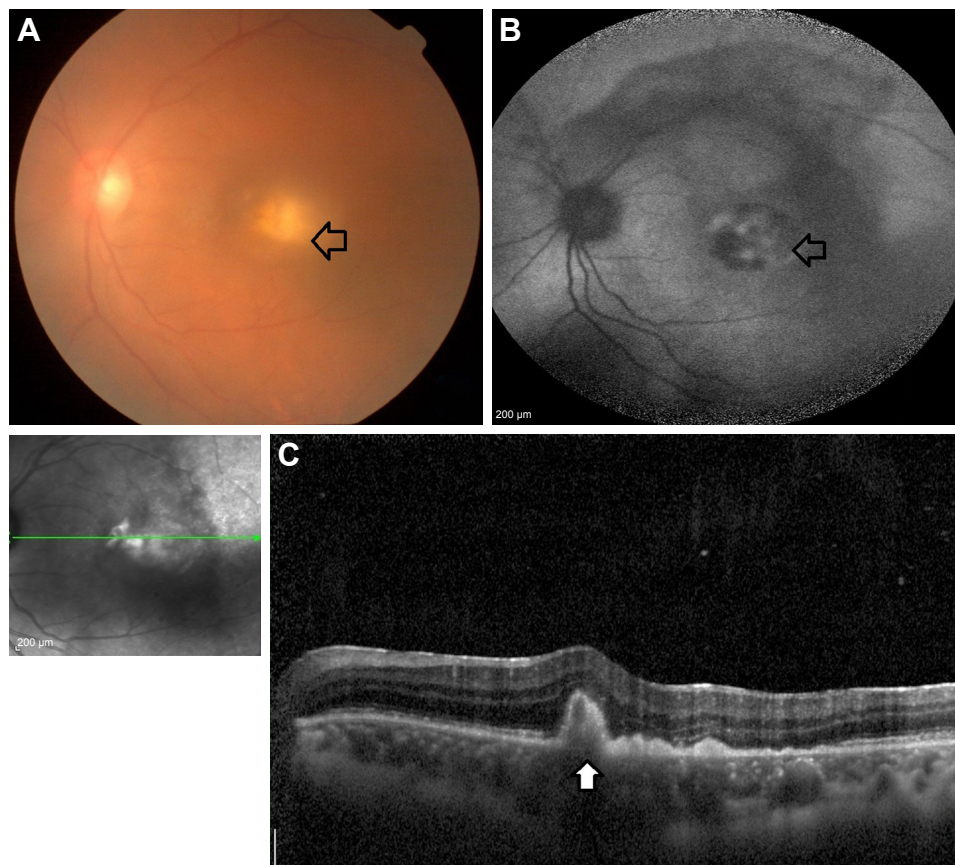
## Clinical features

### Ocular features

PVRL has often been termed as a masquerade syndrome as its clinical signs can mimic a wide variety of ocular diseases. The clinical signs of PVRL vary significantly between patients. The ocular signs are usually bilateral in 64%–83% of the cases, but are often asymmetrical at presentation due to the uneven disease distribution.<sup>3,4</sup> Most patients with PVRL visit the ophthalmologist with symptoms of hazy vision and/or floaters. The ocular symptoms are noticed by the patient long before PVRL is suspected. Some studies have reported the incidence of blurred vision in 40%–50% of cases, decreased visual acuity in 25%–30%, and floaters in 20%–25%.<sup>3,4</sup> Anterior segment findings are less frequently seen compared to posterior segment ophthalmoscopic findings. Anterior segment findings range from a few anterior chamber cells and keratic precipitates<sup>32,33</sup> to the presence of pseudohypopyon,<sup>34,35</sup> and iris and angle infiltration<sup>36,37</sup> in rare cases. Examination of the posterior segment reveals vitritis, ranging from mild-to-severe, in the majority of cases. Visual acuity in most cases of PVRL is better than that expected compared to the extent of vitritis on clinical examination. The lymphoma cells in the vitreous cavity may form clumps, strands, sheets, and membranes with mild-to-severe vitreous haze. Lymphoma cells are homogeneous, larger than inflammatory cells, and do not cluster with reactive cells. This gives an “aurora borealis” like appearance from cells lining along the vitreous fibrils. Creamy lesions with yellowish infiltrates located deep in the retina and/or RPE is another important clinical finding seen in PVRL patients.<sup>21,33,38,39</sup> They can give rise to a characteristic “leopard skin” pigmentation overlying the mass.<sup>40</sup> Other retinal findings include isolated subretinal lesions,<sup>41</sup> exudative retinal detachment,<sup>21</sup> RPE atrophy with subretinal fibrosis, and disciform scarring at the macula (Figures 1A and 2B). Optic nerve infiltration may also occur.<sup>42</sup> In comparison to uveitis cases of similar cellularity, cystoid macular edema is usually absent.

### CNS features

At presentation, 16%–34% of PVRL cases have CNS involvement,<sup>21,43–45</sup> whereas 13%–25% of patients with PCNSL demonstrate ocular findings.<sup>21,46,47</sup> The interval between the onset of ocular or neurological symptoms and a positive diagnosis usually varies from 4 to 40 months, although progression may occur rapidly in some cases.<sup>21,48</sup> Neurological symptoms may occur at any time during the disease course and can be focal and/or diffuse in nature. Symptoms like behavioral changes and alteration in cognitive function, focal neurological deficits like hemiparesis and cerebellar signs, including ataxia, are noted in patients with



**Figure 1** Clinical and imaging features of a patient diagnosed with PVRL. (A) Left eye color fundus image of a 56-year-old male treated with oral corticosteroids for recurrent posterior uveitis with vitritis (2+). An ill-defined yellowish lesion is noted at the posterior pole of the fundus and vitreous biopsy confirmed it is a case of intraocular lymphoma (arrow with black outline). (B) Fundus autofluorescence showing areas of hypo with hyper autofluorescence in the posterior pole of the left eye (arrow with black outline). (C) SDOCT reveals hyperreflective sub-RPE deposits characteristic of intraocular lymphoma (white arrow with black outline).

**Abbreviations:** PVRL, primary vitreoretinal lymphoma; RPE, retinal pigment epithelium; SDOCT, spectral domain optical coherence tomography.

PCNSL. Occurrence of new seizures is a strong indicator of CNS involvement. Infiltration of the meninges by malignant lymphoma cells without intracerebral involvement can also be noted.<sup>49</sup> It is estimated that between 42% and 92% of PVRL cases go on to exhibit intracranial lymphoma within a mean interval of <30 months.<sup>21,43,44,50,51</sup>

## Differential diagnosis

Both infectious and noninfectious uveitis can masquerade as PVRL (Table 1). Systemic malignancies with ocular

metastasis present with multiple focal pale retina lesions with associated exudative retinal detachment and absence of vitreous involvement. Brownish pigmentary mottling overlying the retinal pigment epithelium in these eyes can resemble the “leopard skin” pattern seen in PVRL.

## Imaging findings

### Angiographic imaging

A wide variety of angiographic features have been described in eyes with PVRL. Cassoux et al<sup>21</sup> reported the fluorescein



**Figure 2** Clinical and fluorescein angiography imaging features of a patient diagnosed with PVRL. (A) B-scan ultrasound showing vitreous membranes in the right eye of a patient diagnosed with intraocular lymphoma (arrow with black outline). (B) Right eye color fundus image depicting multiple deep pin-point light yellow lesions spread across the retina (arrow with white outline). (C) Areas of capillary dropout seen on fluorescein angiography (arrow with black outline).

**Abbreviation:** PVRL, primary vitreoretinal lymphoma.

**Table 1** Differential diagnosis of primary vitreoretinal lymphoma

Inflammatory disorders	Infectious diseases	Neoplasms
Intermediate or posterior uveitis or panuveitis	Tuberculosis	Metastatic cancers
Multifocal choroiditis	Endophthalmitis	Amelanotic melanoma
Behcet disease	Toxoplasmosis	
White-dot syndromes	Acute retinal necrosis	
Retinal vasculitis	Syphilis	
Serpiginous chorioretinopathy		
Vogt-Koyanagi-Harada disease		
Sarcoidosis		

angiographic (FA) findings in 44 patients with PVRL. They observed punctate hyperfluorescent window defects in 55% cases of PVRL followed by circular hypofluorescent lesions in 34% and vasculitis in 14%. Angiographically cystoid macular edema was noted in only 2% of cases.<sup>21</sup> Fardeau et al<sup>45</sup> studied the angiographic and topographic features of 53 eyes with cytologically proven diagnosis of PVRL. On FA, numerous small hypofluorescent lesions corresponding to punctate whitish lesions in the fundus were associated with the diagnosis of intraocular lymphoma. Indocyanine green angiography (ICGA) also showed round clustered hypofluorescent lesions at the corresponding areas. The hypofluorescent lesions were identified more in number on FA than ICGA. In conjunction, the FA and ICGA findings had a positive predictive value of 89% and a negative predictive value of 85%<sup>45</sup> (Figure 2C). Other angiographic features like granularity, blockage, late staining at the level of the RPE, and focal areas of capillary nonperfusion have also been described in the literature.<sup>52,53</sup> The hypofluorescent lesions seen on FA in both the early and late phases of the angiogram are mainly due to the accumulation of the lymphoma infiltrates between the retinal pigment epithelium and Bruch membrane, causing blockage of the choroidal fluorescence. The Bruch membrane is impermeable to the lymphoma cells and prevents the malignancy from progressing toward the choroid. This pattern is seen in 45% of eyes with PIOL, compared to 2% of uveitis cases.<sup>45</sup>

### Fundus autofluorescence (FAF)

On FAF images, both hypo- and hyperautofluorescent areas are seen in eyes with PVRL. Hypoautofluorescent areas are suggestive of RPE atrophy or blockage of RPE by the overlying lymphoma cells, whereas hyperautofluorescent spots indicate the overlapping of PVRL and RPE cells. The hyperautofluorescent spots change to hypoautofluorescent spots following treatment with intravitreal methotrexate (Figure 1B). Thus, in recent times, FAF has been used to detect the activity of PVRL and response to treatment.

### Optical coherence tomography (OCT)

Recently, OCT has been utilized in the diagnosis and monitoring treatment in patients with PVRL.<sup>54</sup> On SD-OCT, lymphoma cells appear as nodular elevated lesions underneath the RPE. This is due to the direct focal infiltration of the retina and pre-Bruch membrane space/sub-RPE space by the malignant lymphoma cells.<sup>54,55</sup> Nodular or band hyperreflective spots were noted in 43% of PVRL eyes.<sup>56</sup> Other notable features on spectral domain optical coherence tomography (SDOCT) in eyes with severe PVRL include disruption of the photoreceptor inner segment/outer segment junction, multiple hyperreflective infiltrations within the inner retina, and exudative retinal detachment with subretinal hyporeflective fluid. Cystoid macular edema is not frequently reported. Resolution of the lymphoma deposits along Bruch's membrane was seen on the OCT after intravitreal chemotherapy.<sup>57</sup> This noninvasive method may be convenient for further monitoring of relapse or resolution of PVRL. However, these OCT findings of PVRL needs to be differentiated from those seen in age-related macular degeneration or idiopathic polypoidal choroidal vasculopathy (Figure 1C).<sup>58</sup>

### B-scan ultrasound imaging

The most common findings seen on ophthalmic ultrasound are sheets of vitreous debris, retinal detachment, elevated chorioretinal lesions, and optic nerve widening (Figure 2A). However, none of these changes are specific for PVRL.

### Neuroimaging

In a mean interval of 8–29 months, 42%–92% of PVRL cases presented with intracranial lymphoma.<sup>21,43,44,50,51</sup> Thus, it is imperative for every patient to undergo contrast-enhanced MRI on a regular basis during the disease course after the definitive diagnosis of PIOL has been made.<sup>59</sup> MRI helps in identifying CNS involvement and in monitoring the treatment response of neurological lesions following high-dose systemic chemotherapy. On MRI, lymphoma lesions appear hypodense on T1-weighted and hyperdense on T2-weighted scans with discrete or diffuse borders.<sup>47</sup> Positron emission tomography/computed tomography has been used to identify both CNS and ocular activity, both of which take up the 2-[(18)F] fluoro-2-deoxy-D-glucose dye.<sup>57</sup>

The characteristic features of different imaging modalities are mentioned in Table 2.

### Biopsy

#### Ocular tissue biopsy

Identification of the malignant lymphoid cells in ocular tissue using biopsy still remains the cornerstone of diagnosis and

**Table 2** Imaging modalities used and their descriptive findings in the diagnosis and monitoring of PVRL

Imaging modality	Utility	Imaging features
• Fluorescein Angiography (FA)	Diagnosis	<ul style="list-style-type: none"> <li>• Punctate hyperfluorescent lesions</li> <li>• Circular hypofluorescent lesions</li> <li>• Vasculitis</li> <li>• Cystoid macular edema</li> <li>• Other features like granularity, blockage, late staining at the RPE level, and focal areas of capillary non-perfusion</li> </ul>
• Indocyanine green angiography (ICGA)	Diagnosis	<ul style="list-style-type: none"> <li>• Early hypofluorescent lesions with late staining</li> </ul>
• Fundus autofluorescence (FAF)	Disease activity and treatment monitoring	<ul style="list-style-type: none"> <li>• Hypo FAF lesions</li> <li>• Hyper FAF lesions</li> </ul>
• Optical coherence tomography (OCT)	Disease activity and treatment monitoring	<ul style="list-style-type: none"> <li>• Sub-RPE nodular elevated lesions</li> <li>• Other features like disruption of the photoreceptor inner segment/outer segment junction, multiple hyperreflective infiltrations within the inner retina, exudative retinal detachment with subretinal hyporeflective fluid, and cystoid macular edema</li> </ul>
• B-scan ultrasound imaging	Treatment monitoring	<ul style="list-style-type: none"> <li>• Sheets of vitreous debris</li> <li>• Retinal detachment</li> <li>• Elevated chorioretinal lesions</li> <li>• Optic nerve widening</li> </ul>
• Neuroimaging	CNS metastasis	<ul style="list-style-type: none"> <li>• Hypodense on T1-weighted and hyperdense on T2-weighted scans with discrete or diffuse borders</li> </ul>

**Abbreviations:** CNS, central nervous system; PVRL, primary vitreoretinal lymphoma; RPE, retinal pigment epithelium.

treatment in malignant lymphomas, including PVRL.<sup>60,61</sup> Usually, vitreous biopsy either by vitrectomy or direct vitreous aspiration is performed, especially when CSF evaluation is negative or when intracranial lymphoma lesions are not identified on neuroimaging. Clinically, pars plana vitrectomy is better than vitreous aspirate as it provides a superior diagnostic yield.<sup>61</sup> In addition, pars plana vitrectomy helps in improving vision by clearing the vitreous debris and maximizing the sample size,<sup>60,61</sup> although extension of the lymphoma through the sclerotomy port to the epibulbar space following vitrectomy may occur.<sup>62</sup> A small gage transconjunctival sutureless vitrectomy performed using the 25 G or 27 G instrumentation is a safe and effective technique for the diagnosis of PVRL.<sup>63</sup> A low cut rate of 600 cpm is recommended in order to obtain a higher diagnostic yield and more viable lymphoma cells.<sup>64</sup> Routinely, both the undiluted vitreous (1–2 mL) and diluted vitreous samples are obtained as much as possible after turning on the infusion. Retinal biopsy is seldom used clinically, and retinal samples are usually taken from the deeper part of the lesion, near the choriocapillaris, where viable lymphoma cells are most likely to be found.<sup>61</sup> Aqueous aspirate is used in special conditions, such as pseudohypopyon. It is important to transfer the sample immediately to the pathologist once it has been obtained. Biopsy results have a high false-negative rate (about 70%). This is mainly due to the poor sample volume, paucicellular specimens, and necrotic lymphoma cells. Hence, more than

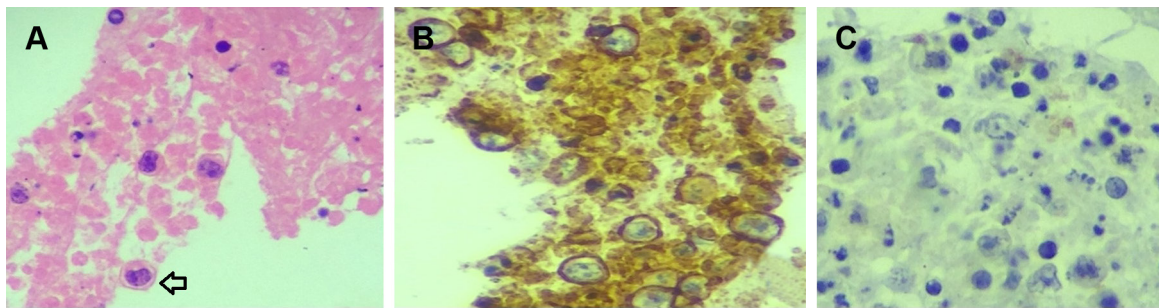
one biopsy is often required to make a confident diagnosis in PVRL cases.<sup>5</sup> In many cases, the paucity of the cells in the biopsy specimens may be the result of corticosteroid treatment, which must be discontinued for at least 2 weeks before the procedure.<sup>65</sup>

### Cerebrospinal fluid

CSF is obtained in cases with suspected PCNSL. About 25% of patients with identifiable lesions on MRI will have positive CSF cytology.<sup>66,67</sup> If a diagnosis of PCNSL can be made from the identification of lymphoma cells in CSF, and there is simultaneous ocular involvement, then the patient is spared from the need for invasive ocular tissue biopsy for diagnosis.

### Cytology and histopathology

The diagnosis of PVRL requires a multi-disciplinary approach. The pathologist's role is to accurately identify the malignant lymphoma cells on the basis of morphology, and then to assess the clonality using immunocytochemistry and molecular techniques like flow cytometry and PCR analysis. Morphologically, the typical lymphoma cells are large B-cell lymphoid cells with a scanty basophilic cytoplasm, an increased nucleus:cytoplasm ratio, with hypersegmented, multivariable-shaped nuclei, multiple nucleoli, and a coarse chromatin pattern.<sup>43,44,68,69</sup> The correlation between pathological diagnosis and clinical diagnosis on long-term follow-up is as high as 96%.<sup>44</sup> Davis et al<sup>70</sup>



**Figure 3** Cytopathology images of a case of PVRL. (A–C) Vitreous sample smeared and stained with H&E and Giemsa stains showing a moderately cellular lymphoid cell population with abundant atypical lymphoid cells that are large, hyperchromatic prominent nucleoli and scanty cytoplasm (arrow with black outline). Also seen are mature, small, and intermediate size lymphocytes accompanying these atypical lymphoid cells. No granuloma is seen. Immunohistochemistry shows atypical lymphoid cells with CD 20 membrane positivity.

**Abbreviation:** PVRL, primary vitreoretinal lymphoma.

studied the vitreous sample using cytology evaluation, flow cytometry, and culture techniques in 28 patients with suspected intraocular lymphoma based on their clinical features. Vitreous evaluation confirmed the diagnosis of PVRL in 14 of the 28 (50%) patients. Thirteen out of the 27 vitreous samples that underwent cytological evaluation tested positive for lymphoma. In only four samples with positive cytological evaluation, the clinical diagnosis of lymphoma was confirmed. In the remaining ten eyes with confirmed diagnosis of lymphoma, cytology was unable to identify the abnormal malignant lymphoid cells. Thus, for lymphoma, the positive predictive value of cytologic evaluation was 30.8% (95% CI=12.7–57.6) and the negative predictive value was 33.3% (95% CI=15.2–58.3).<sup>70,71</sup> This is due to the sparse number of cells in vitreous sample and the contamination of the vitreous specimen with other cellular structures like reactive T-lymphocytes, necrotic cells, debris, and fibrin.<sup>44</sup> Molecular testing of vitreous in 80 eyes of PVRL showed the IL-10:IL-6 >1 in 56 out of 80 eyes; 53/56 had the correct diagnosis of PVRL. In 24 eyes with IL-10:IL-6 <1, 17 eyes had the correct diagnosis of uveitis. Thus, the positive predictive value of molecular testing for lymphoma was 94.6% (95% CI=85.4–98.5) and the negative predictive value was 70.8% (95% CI=50.8–85.1).<sup>71</sup> In cases with scanty cytology, phenotyping of cells by their surface markers are useful in identifying the lymphomatous cells. Immunocytological techniques use a cell-mounted slide with antibodies directed at specific cell markers (Figure 3).<sup>72,73</sup> In flow cytometry, the cells are separated using a fluorescence activated cell sorter in a fluid medium. Immunocytology increases the rate of diagnosis from 30% (using cytology alone) to 70%<sup>74</sup> but requires more cells. Flow cytometry allows for multiple monoclonal antibodies to be applied to an aliquot of suspected lymphoma cells simultaneously,

which allows the use of a larger detection panel.<sup>75–77</sup> In B-cell lymphomas, a B-cell population stains positively for B-cell markers (CD19, CD20, or CD22) with restricted expression of either  $\kappa$  or  $\lambda$ . In T-cell lymphomas, the T-cell population stains positively for T-cell markers (CD3, CD4).<sup>57</sup> A ratio of  $\kappa$ : $\lambda$  of >3 or <0.6 is useful as a marker for clonality.<sup>57</sup>

### PCR analysis

Immunoglobulin heavy chain (IgH) gene sequences, particularly in the third complementarity-determining region (CDR3) of the variable region of IgH and T-cell receptor gene rearrangements have been used in assessing the clonal expansion of B and T lymphocytes, respectively. Studies using PCR on systemic B-cell lymphoma<sup>78</sup> and in PIOL<sup>79–81</sup> reveal rearrangement of IgH gene and bcl-2 proto-oncogene translocations. Cellular microdissection and PCR amplification can be applied together if malignant cells are too scanty to yield a greater cell population from vitreous specimens.<sup>71,81–83</sup> Wang et al,<sup>71</sup> in 114 cases of B-cell PIOL using this technique, showed rearrangement of the CDR3 of IgH gene in all, but this change was found in only one of 86 cases of uveitis. PCR-based studies have suggested that the B-cells of PIOL are mature B-cells that have undergone the germinal center reaction and the identical clone can be identified in ocular and cerebral tissues in cases of CNS involvement.<sup>84</sup>

### Biochemical tests

High levels of IL-10 are produced by B-cell lymphomas. IL-10 is a Th2 cytokine and linked to rapid disease progression. Normal inflammatory cells secrete high levels of IL-6.<sup>4,85</sup> Chan et al<sup>86</sup> were the first to report high levels of vitreous IL-10 in three B-cell PVRL patients. IL-10 is elevated in the presence of malignant B-lymphocytes in PIOL/PCNSL, whereas IL-6 or IL-12 is elevated in inflammatory states.<sup>86–89</sup>

Higher IL-10 levels have been correlated with more aggressive disease.<sup>90</sup> Currently, a IL-10:IL-6 ratio  $>1$  in ocular fluid has become an adjunctive and supportive biomarker for the diagnosis and prognosis of PVRL, particularly the B-cell PVRL.<sup>4,57</sup>

## Blood tests

Blood investigations should be done to rule out other causes of infectious and noninfectious uveitis.<sup>91</sup> Additionally a complete blood count and HIV virus testing is useful.<sup>18</sup>

## Others

The presence of MYD88 mutations, especially L265P, are very frequent in VRL, and their detection significantly improves the diagnostic yield of vitrectomy specimens.<sup>92,93</sup>

The interpretation of any test should be done in the context of clinical findings and should involve a multidisciplinary approach.

## Treatment

PVRLs are radiosensitive and chemosensitive tumors. The overall mortality rate of PVRL is quite high, ranging between 9% and 81% in follow-up periods ranging from 12 months to 35 months.<sup>3,25,38,43</sup> A professional team of experts in ophthalmology, oncology (particularly neuro-oncology or hematologist), and pathology are essential for optimizing patient management.<sup>85</sup> The International Primary CNS Lymphoma Collaborative Group in 2011 recommended the guidelines for the treatment and follow-up of patients with PVRL with/without PCNSL.<sup>4</sup> In 2015, the European Association of neuro-oncologists laid the guidelines for the diagnosis and treatment of PCNSL<sup>94</sup> (Figure 4). As per the recent guidelines, the first line of treatment of PIOL is high-dose systemic chemotherapy along with intravitreal chemotherapy and/or ocular radiotherapy, even in the absence of PCNSL.

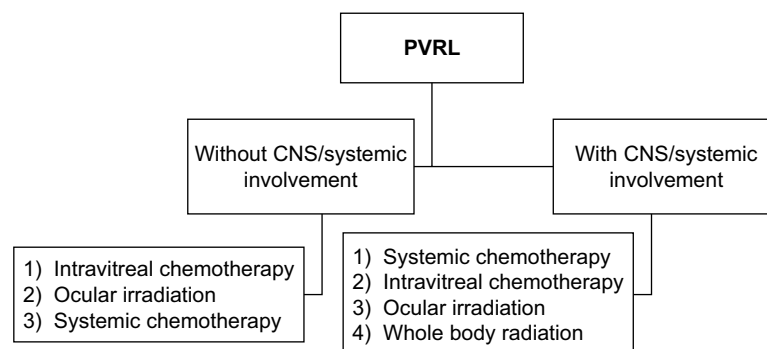
In patients with contraindications for systemic chemotherapy or for elderly patients with relapsing intraocular disease, local treatment alone (intravitreal chemotherapy or ocular radiotherapy) is an acceptable and valid approach.<sup>94</sup>

## Radiotherapy

Ocular irradiation using low-dose external beam radiotherapy has been recommended as local treatment for ocular only PVRL patients.<sup>4</sup> Berenbom et al<sup>25</sup> treated 12 patients of PVRL with radiotherapy at a dose of 30–35 Gy in 15 fractions during a mean follow-up of 19 months. No ocular relapses were reported in any of these patients. If PVRL patients having concurrent CNS involvement failed systemic chemotherapy and were also unavailable to aggressive therapy, whole brain and eye radiotherapy may be added. The complication of whole brain radiation often induces a delayed neurotoxicity with a decrease in cognitive function, ataxia, and sometimes even death, whereas ocular complications were cataract, dry eye, and radiation retinopathy.<sup>25,95</sup> Currently, whether to use intravitreal chemotherapy or ocular radiation as first-line therapy is still controversial.

## Systemic chemotherapy

High-dose chemotherapy with intravenous methotrexate is the first line agent used in the treatment of patients with PVRL with CNS or systemic involvement. The efficiency of high-dose methotrexate is demonstrated to produce a remission rate of up to 72% when used alone, and up to 94%–100% in combinations.<sup>43,78</sup> Median survival improved from 28 to 85 months in the high-dose chemotherapy group.<sup>96</sup> High dose chemotherapy with thiotepa, busulfan, and cyclophosphamide, followed by autologous peripheral blood stem cell transplantation, is reserved for cases demonstrating relapse or refractory response.<sup>96–99</sup> Recurrent PIOL with PCNSL has been treated with intrathecal methotrexate and cytarabine.<sup>98,100</sup>



**Figure 4** Treatment algorithm for PVRL.

**Abbreviations:** CNS, central nervous system; PVRL, primary vitreoretinal lymphoma.

Oral trofosphamide or intravenous iraphosphamide may produce 6–18 months of progression-free survival.<sup>101–104</sup>

The IELSG32 trial provided a high level of evidence supporting the use of MATRix combination (methotrexate, cytarabine, thiotepa, and rituximab) as the new standard chemoimmunotherapy for patients aged up to 70 years with newly diagnosed primary CNS lymphoma.<sup>105</sup> At median follow-up of 30 months (IQR = 22–38), patients treated with MATRix regime had a complete remission rate of 49% (95% CI =38–60), compared with 23% (14–31) of those treated with methotrexate-cytarabine alone (HR =0.46, 95% CI =0.28–0.74), and 30% (21–42) of those treated with methotrexate-cytarabine plus rituximab (0.61, 0.40–0.94).

## Role of systemic chemotherapy and/or irradiation to prevent CNS involvement

In a study by Hormigo et al<sup>106</sup> to investigate the role of prophylactic aggressive therapy for ocular only disease, 17 PVRL patients treated with chemotherapy and/or irradiation had a median survival period of 60 months after onset of ocular symptoms, compared to 35 months for 14 patients treated only after CNS disease developed. Another study also demonstrated that prophylactic systemic chemotherapy did not inhibit, but did significantly delay the onset of CNS involvement in PVRL patients.<sup>107</sup>

## Ocular chemotherapy

Two local chemotherapy agents used in the treatment of PVRL are intravitreal methotrexate and intravitreal rituximab.

### Intravitreal methotrexate

Local tumor control can be achieved with intravitreal chemotherapy with methotrexate at a dose of 400 µg in 0.1 mL in relapsed PIOL,<sup>108–110</sup> in ocular relapse of PCNSL,<sup>111</sup> and as a primary treatment in combination with systemic chemotherapy,<sup>112</sup> intrathecal chemotherapy,<sup>113</sup> or sub-Tenon steroid injections.<sup>114</sup> The schedule for intravitreal methotrexate injections was bi-weekly for 4 weeks, every week for 8 weeks, and then monthly for 9 months, comprising a total of 25 injections. Remission was usually reached after a mean of 6.4 injections, with only 5% of the eyes requiring ≥13 injections. In a 10-year study using intravitreal injections of methotrexate as first line treatment in PVRL, none of the total 26 patients had an intraocular recurrence.<sup>115</sup> The common complications were transient intraocular pressure elevations and corneal epitheliopathy.<sup>85,116</sup>

### Intravitreal rituximab

Rituximab is an anti-CD20 monoclonal antibody, used recently to treat CD20-positive PVRL.<sup>96</sup> Intravitreal injections of 1 mg/0.1 mL-rituximab weekly for 4 weeks as a one-course protocol showed encouraging results in 20 eyes with CD20-positive PVRL. However, 50% of the cases showed recurrences in the study.<sup>117</sup> Relapses following intravitreal rituximab may require treatment with intravitreal methotrexate and radiation.<sup>118</sup> Rituximab may be a less toxic alternative to methotrexate.

### Newer emerging therapies

In recent times, research groups have been testing newer innovative methods for treating PIOL. This includes the use of membrane FasL vesicles, the membrane-only form of Fas ligand, to activate innate immunity and terminate the immune privilege of the eye.<sup>119</sup> Recombinant immunotoxin therapy is an emerging immunotherapeutic approach, where a single intravitreal injection of immunotoxin HA22 into eyes of a mouse model of intraocular lymphoma resulted in complete regression of the tumor, demonstrating B-cell-specific immunotoxin therapy.<sup>120,121</sup> Other monoclonal antibodies, such as daclizumab, efalizumab, and alemtuzumab, showed positive results in animal models, and had the potential for useful adjuvant therapy for ocular lymphoma.<sup>122</sup> Venetoclax, a BCL-2 inhibitor, has been used for the treatment of patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), or diffuse large B-cell lymphoma.<sup>123</sup> The use of stem cell transplantation for PVRL has been described in the literature. However, limited data is available on the use of high-dose chemotherapy and autologous stem cell transplantation in the treatment of PVRL, with most trials either including only PCNSL or combining PCNSL with PVRL. The results of autologous stem cell transplantation in the treatment of PVRL seems to be promising, and can be considered mainly for refractory and recurrent cases of PVRL.<sup>96–99,124</sup> Newer drugs like pomalidomide,<sup>125</sup> ibrutinib,<sup>126</sup> and a combination of lenalidomide and rituximab<sup>127</sup> have also been tried in the treatment of PCNSL and PVRL.

## Prognosis

The diagnosis of PVRL is often delayed. The delay in the diagnosis is due to the late presentation to the ophthalmologist. Most patients of PVRL present persistent floaters affecting their visual quality with relatively better visual acuity. The reporting of mortality in the literature is inconsistent due to variations in patient populations, variation in treatment regimens, and small case series. Mortality rates range between



9% and 81% in follow-up periods, ranging from 12 to 35 months.<sup>3,25,38,43</sup> In PCNSL, median survival of patients treated with radiotherapy with/without chemotherapy ranged from 10 to 16 months, which can be extended to greater than 30 months with methotrexate-based chemotherapy<sup>128</sup> or by ifosfamide or trofosfamide.<sup>105</sup> Grimm et al<sup>67</sup> reported a median progression-free interval of 18 months and overall survival period of 31 months in 221 patients with PCNSL with intraocular involvement collected from 16 centers in seven countries receiving a mix of therapies. They concluded that ocular therapy improved local tumor control but had no effect on survival. In contrast, another series found a survival advantage if PIOL was diagnosed before CNS involvement 60 months survival vs 35 months, although the group with initial ocular diagnosis was younger.<sup>95</sup>

## Conclusion

PVRL is a masquerading ocular disease, making it difficult to diagnose and treat. With recent advances in diagnostic imaging and molecular techniques, the detection of this highly aggressive disease has improved. High relapse rates and CNS involvement are common, which result in poor prognosis of PVRL, despite aggressive treatment with chemotherapy and/or radiotherapy. Further, with the advent of new targeted therapies for both PVRL and PCNSL, there is hope that, if PVRL is detected sufficiently early, the prognosis will improve. Collaborative multicenter efforts are essential to improve data collection to have a better understanding of the pathogenesis and biology of this disease. In PVRL, despite the multiple encouraging diagnostic and therapeutic advances that have been achieved, the optimal standard clinical diagnosis and treatment strategies still merit further research.

## Disclosure

The authors report no conflicts of interest in this work.

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