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## Major review

Primary intraocular lymphoma<sup>☆</sup>

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## ABSTRACT

Primary intraocular lymphoma (PIOL) is an ocular malignancy that is a subset of primary central system lymphoma (PCNSL). Approximately one-third of PIOL patients will have concurrent PCNSL at presentation, and 42–92% will develop PCNSL within a mean of 8–29 months. Although rare, the incidence has been rising in both immunocompromised and immunocompetent populations. The majority of PIOL is diffuse large B-cell lymphoma, though rare T-cell variants are described. Recently, PIOL has been classified by main site of involvement in the eye, with vitreoretinal lymphoma as the most common type of ocular lymphoma related to PCNSL. Diagnosis remains challenging for ophthalmologists and pathologists. PIOL can masquerade as noninfectious or infectious uveitis, white dot syndromes, or occasionally as other neoplasms such as metastatic cancers. Laboratory diagnosis by cytology has been much aided by the use of immunocytochemistry, flow cytometry, biochemical finding of interleukin changes (IL10:IL6 ratio > 1), and cellular microdissection with polymerase chain reaction amplification for clonality. Use of several tests improves the diagnostic yield. Approaches to treatment have centered on systemic methotrexate-based chemotherapy, often with cytarabine (Ara-C) and radiotherapy. Use of intravitreal chemotherapy with methotrexate (0.4 mg/0.1 mL) is promising in controlling ocular disease, and intravitreal rituximab (anti-CD20 monoclonal antibody) has also been tried. Despite these advances, prognosis remains poor.

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## 1. Background

The designation intraocular lymphoma represents a heterogeneous group of malignant lymphocytic neoplasms arising from either within the central nervous system (primary central nervous system lymphoma - PCNSL) or outside the central nervous system as metastasis from a non-ocular neoplasm (secondary intraocular lymphoma).<sup>6</sup> Primary intraocular lymphoma (PIOL) is a subset of PCNSL where there is intraocular involvement. Diagnosis poses a challenge to ophthalmologists and pathologists alike, as the disease can masquerade as steroid-resistant ocular inflammation.<sup>171,174</sup> Although a rare occurrence, the incidence of PIOL has increased in the past 15 years, and prognosis for life remains poor. We provide a comprehensive summary of the current literature available on primary intraocular lymphoma and highlight areas where further research is required.

## 2. Definition

### 2.1. Primary intraocular lymphoma (PIOL)

Primary intraocular lymphoma (PIOL) was initially defined as a subset of primary central nervous system lymphoma in which lymphoma cells occur initially only in the eyes, without evidence of disease in the brain or cerebrospinal fluid,<sup>22,32</sup> although concomitant as well as subsequent intracranial involvement occurs in many cases.<sup>37,54</sup> The lymphoma cells are seen within the vitreous and retina.

### 2.2. Secondary intraocular lymphoma

Secondary intraocular lymphoma arises outside the central nervous system and metastasizes to the eye.<sup>22,84,94,142</sup> The secondary type, which typically has different clinical features and prognosis,<sup>32</sup> is outside the scope of the present review. The lymphoma cells are present mainly in the uvea. Ocular relapse of lymphoma of the testes, another immune-privileged site, has been reported to mimic PIOL.<sup>207</sup> Systemic T-cell lymphoma with intraocular involvement shares some of the ocular clinical features of typical B-cell PIOL.<sup>132,135</sup>

## 3. Historical aspects

### 3.1. First description

The entity now known as PIOL was called malignant lymphoma of the uveal tract, by Cooper in 1951<sup>47</sup> and Givner in 1955.<sup>91</sup> This terminology was replaced by the designation ocular reticulum cell sarcoma.<sup>130</sup>

### 3.2. Early descriptions

Klinge and Hogan reported eight cases of ocular reticulum cell sarcoma, four of which were diagnosed by craniotomy when the signs of a brain tumor developed.<sup>130</sup> A further report detailed the use of radiotherapy to the eyes for local tumor

control and to improve vision and radiotherapy to the brain because of frequent intracranial involvement.<sup>144</sup>

### 3.3. Current World Health Organization classification and general overview of lymphoma nomenclature

Hematopoietic and lymphoid tissue tumors are classified by the World Health Organization categories that include myeloid, lymphoid, and histiocytic neoplasms. The system uses the Revised European-American Lymphoma (REAL) classification and is based on the principle that a classification is a list of “real” disease entities that are defined by a combination of morphology, immunophenotype, and genetic and clinical features.<sup>101,102</sup>

Broadly speaking, the classification divides primarily into Hodgkin and non-Hodgkin lymphoid neoplasms. The latter has two major categories: B-cell and T-/natural killer cell neoplasms. The T- and B-cell neoplasms are further stratified into lymphoblastic (precursor cell) and mature (peripheral) B- and T-cell neoplasms. The latter are grouped according to clinical presentation—leukemic (disseminated) and primary extranodal and predominantly nodal (solid). The classification considers lymphomas and lymphocytic leukemias of the same cell type as one disease with different clinical presentations.<sup>101</sup> Most PIOLs are of B-cell origin, and fall within the category of diffuse large B-cell lymphomas.<sup>41,65,216</sup> Isolated PIOLs of T-cell origin occur rarely.<sup>17,25,50,86,92</sup> Extranodal marginal zone lymphoma (mucosa associated lymphoid tissue B-cell lymphomas) can also present with intraocular features, often with a localized uveal mass with extraocular extension, and is termed primary uveal lymphoma.<sup>46,53,56,59</sup>

## 4. Epidemiology

The exact epidemiology of PIOL, a rare malignancy, is not known, and most data relate to the larger group of primary central nervous system (CNS) lymphoma. These are estimated to represent 4–6% of primary brain tumors and 1–2% of extranodal lymphomas.<sup>85,106</sup> The incidence in the USA has tripled over the past 15 years,<sup>72,106,177</sup> and this rise has been mirrored in Europe.<sup>123</sup> This increase was initially thought to be due to increased numbers of immunocompromised patients, but since the introduction of highly active antiretroviral therapy, the incidence in patients with the acquired immune deficiency syndrome (AIDS) has declined.<sup>93,155,172,189</sup> Iatrogenic immunosuppression may also lead to PIOL.<sup>39,49,120,126,173,218</sup> The cause for the increased incidence in immunocompetent patients is unknown.<sup>155</sup> The Central Brain Tumor Registry of the United States for the period 1998–2002 suggests that the incidence of CNS lymphoma has dropped to 3.1% of brain tumors.<sup>29</sup>

PIOL usually occurs in adults from the third to the eighth decades of life,<sup>19,27,107</sup> although cases in infants<sup>39,211</sup> and adolescents are documented.<sup>163,183</sup> The mean age of presentation is in the fifth and sixth decades of life.<sup>19,51,85,163,213</sup> Some reports suggest a sex bias, with women more commonly affected than men by 2:1<sup>15,21,163</sup> or even greater.<sup>27,168</sup> More recently there appears to have been an increase of reported

cases in men.<sup>168</sup> There appears to be no racial predilection for the disease.

## 5. Etiology

The etiology of PIOL/PCNSL remains an enigma. One hypothesis suggests that in immunocompromised patients, a mutation in the Epstein-Barr virus attracts lymphocyte cells to the CNS, where transformation to neoplastic cells is initiated.<sup>144</sup> This is supported by the finding that Epstein-Barr virus is invariably found in AIDS patients with PCNSL and usually runs a more aggressive course,<sup>101</sup> but the same association is not documented in PIOL.<sup>160</sup> *Toxoplasma gondii* DNA has also been found in B-cell lymphoma cells in 2 out of 10 PIOL samples, leading to speculation on the role of this organism.<sup>181</sup> One suggestion is that an infectious antigen driven B-cell expansion is the primary trigger, which then becomes clonal.<sup>30</sup> Another hypothesis poses haematological transfer of neoplastic cells from nodal and extranodal sites to ocular and central nervous system structures.<sup>21</sup> In the chemokine hypothesis, B-cell chemokines may selectively attract lymphoma cells from the choroidal circulation to the retinal pigment epithelium (RPE). The B-cell chemokine receptors CXCR4 and CXCR5 were detected in lymphoma cells, whereas their ligands BLC and SDF-1 were detected only in the RPE.<sup>35</sup> A disturbance in the factors contributing to the immune privilege of the eye has also been implicated.<sup>31</sup>

## 6. Clinical features

### 6.1. Ocular features

One of the difficulties in the diagnosis of PIOL is its tendency to mimic chronic posterior uveitis, even to the extent of an initial response to steroid therapy. Symptoms at presentation include blurred vision and/or floaters, but visual acuity is usually better preserved than would be expected.<sup>21,37,107,133,213</sup>

Anterior segment inflammatory findings are frequently absent,<sup>27</sup> particularly scleral redness or posterior synechiae. There may be cells in the anterior chamber and the presence of keratic precipitates.<sup>22,54</sup> Rare cases can present with infiltration of the iris or angle<sup>39,202</sup> or as a pseudohypopyon.<sup>48,138</sup>

Examination of the posterior segment (Fig. 1) reveals vitritis, which is present in the majority of cases.<sup>2,6,42,163</sup> Vitreous cells may form clumps, sheets, or strands with mild to moderate haze. Another sign is the development of creamy lesions with orange-yellow infiltrates that are deep to the retina or RPE.<sup>2,6,22,27,42,88,110</sup> They can give rise to a characteristic “leopard skin” pigmentation overlying the mass.<sup>88</sup> There may be isolated subretinal lesions,<sup>134</sup> sometimes with associated exudative retinal detachment.<sup>27</sup> Spontaneous resolution may lead to RPE atrophy with subretinal fibrosis.<sup>68</sup> Cystoid macular edema is often absent, in contrast to uveitis cases of similar cellularity,<sup>77</sup> and vision is better than expected from the degree of vitritis. The vitreoretinal form of the disorder can mimic choroiditis or vasculitis.<sup>10,19</sup> Optic nerve infiltration may occur.<sup>90,103</sup> Ocular disease is bilateral in 64–83% of cases, although initially it may seem unilateral.<sup>27,42,107,163</sup> Orbital



**Fig. 1 – Composite color fundus photograph of the left eye of a patient with PIOL. Note the hazy appearance of the fundus due to the presence of vitreous cells, marked yellow subretinal infiltrates with overlying retinal pigment epithelial changes (“leopard spotting”) and accumulation of subretinal fluid. Vitreous tap failed to provide sufficient cells for diagnosis, so a vitrectomy with retinotomy and subretinal aspirate was required to diagnose PIOL.**

involvement in PIOL is exceptionally rare.<sup>149,157</sup> Parikh et al reported a systemic non-Hodgkin lymphoma simulating PIOL with vitritis and a subretinal lesion, but without the choroidal involvement typical of secondary intraocular lymphoma.<sup>162</sup> The delay between a positive diagnosis and the onset of ocular or neurological symptoms usually varies from 4–40 months,<sup>27,99,107</sup> although rapid progression may occur.<sup>204</sup>

### 6.2. CNS features

Symptoms of CNS involvement may emerge at any time of the disease course and can be focal and/or diffuse.<sup>2,21,108,163,168</sup> At presentation of PIOL, 16–34% have CNS involvement.<sup>2,27,51,77</sup> Tumors of the frontal lobe can induce behavioral changes and alteration in cognitive function.<sup>10,98</sup> Common focal neurological findings are hemiparesis in 51% and cerebellar signs, including ataxia, in 23%.<sup>106</sup> A strong indicator of CNS involvement is new-onset seizures.<sup>90</sup> Lymphomatous meningitis without intracerebral involvement is one variant.<sup>111</sup>

From 13% to 25% of patients with PCNSL have ocular signs on diagnosis.<sup>27,80,104</sup> Conversely, it is estimated that between 42% and 92% of PIOL cases go on to exhibit intracranial lymphoma within a mean interval of 8–29 months.<sup>2,27,51,85,163</sup> Widespread dissemination of PCNSL can also occur in 7–8% of patients, usually late in the course.<sup>104</sup>

### 6.3. Primary uveal lymphoma

This less common entity involves any region of the uveal tract locally. These were previously misnamed “reactive lymphoid hyperplasia” and “uveal pseudotumors,” underlining their less-aggressive clinical course.<sup>53,56</sup> Cockerham and associates re-evaluated pathological specimens of benign choroidal reactive lymphoid hyperplasia archived at the Armed Forces

Institute of Pathology and found 80% of these to be low-grade B-cell lymphomas by histology, immunocytochemistry, and polymerase chain reaction,<sup>46</sup> and the subtype is of an extra-nodal marginal zone or mucosa associated lymphoid tissue lymphoma.<sup>53</sup> These eyes harbor a pale choroidal mass, rather than the vitreoretinal involvement that occurs with PIOL. Primary uveal lymphomas typically remain stable and produce minimal symptoms; if treatment is required, they are very radiosensitive and carry a good prognosis.<sup>46,56</sup> There is often accompanying extraocular extension.<sup>53,156</sup>

We will concentrate on primary intraocular lymphoma of the diffuse large B-cell type. Recently, there has been a suggestion to replace the term PIOL with the anatomical location of the lymphomatous infiltrates, namely, vitreoretinal, uveal, iridal, or ciliary body.<sup>52</sup>

#### 6.4. Differential diagnosis of PIOL

As it is a “masquerade syndrome”<sup>10,27,54,76,100,123</sup> (Table 1), the differential diagnosis of PIOL is wide and includes both infectious<sup>5,8,27,44,70,87,96,147,154,161,178</sup> and noninfectious uveitis.<sup>20,27,29,75,90,170,180,206</sup> Metastatic cancers are usually pale choroidal lesions associated with subretinal fluid in the absence of vitreoretinal involvement. Sometimes metastases with overlying mottled brown pigmentation at the level of the retinal pigment epithelium mimic the “leopard skin” appearance seen in PIOL. Amelanotic melanoma is also in the differential diagnosis. Even in the over-60-years age group with new-onset uveitis, PIOL remains a rare disorder.<sup>12,43,151</sup>

## 7. Diagnostic techniques in PIOL

### 7.1. Imaging

#### 7.1.1. Ocular

**7.1.1.1. Fluorescein and indocyanine green angiography.** In 44 patients with PIOL undergoing fluorescein angiography,<sup>27</sup> there were punctate hyperfluorescent window defects in 55%, round hypofluorescent lesions in 34%, and vasculitis in 14%, although only 2% had angiographic evidence of cystoid macular edema. A National Eye Institute study of 17 patients with PIOL found granularity, blockage, and late staining at the level of the RPE, with a notable lack of other angiographic signs of inflammation such as macular edema and perivascular staining or leakage.<sup>201</sup> In another series,<sup>77</sup> small well-defined hypofluorescent lesions corresponding to the infiltrates were seen in the early and late phases, indicating masking of the choroidal fluorescence, a pattern present in 45% of PIOL eyes, compared with 2% of the uveitis cases.

Indocyanine green angiography showed small hypofluorescent lesions in the early phase, becoming less apparent in the late phases. The hypofluorescent lesions were more numerous on fluorescein than indocyanine green angiography.<sup>77</sup> Together, the fluorescein and indocyanine green angiographic findings had a positive predictive value of 89% and a negative predictive value of 85%.<sup>77</sup> (Fig. 2).

**7.1.1.2. Fundus autofluorescence.** In 5 eyes with PIOL the clinically observed brown “leopard spotting” over yellow

**Table 1 – The Differential diagnosis of primary Intraocular lymphoma**

Inflammatory disorders
Posterior or intermediate uveitis or panuveitis
Multifocal choroiditis
Behçet disease
Acute posterior multifocal placoid pigment epitheliopathy (AMPPE)
Multiple evanescent white dot syndrome
Birdshot choroidopathy
Serpiginous chorioretinopathy
Retinal arterial and venous obstruction or vasculitis
Frosted branch angiitis
Vogt-Koyanagi-Harada disease
Sarcoidosis
Infectious causes
Tuberculoma
Cytomegalovirus retinitis
Endophthalmitis
Herpetic uveitis
Toxoplasmosis
Acute retinal necrosis
Syphilis
Neoplasms
Metastatic cancers
Amelanotic melanoma

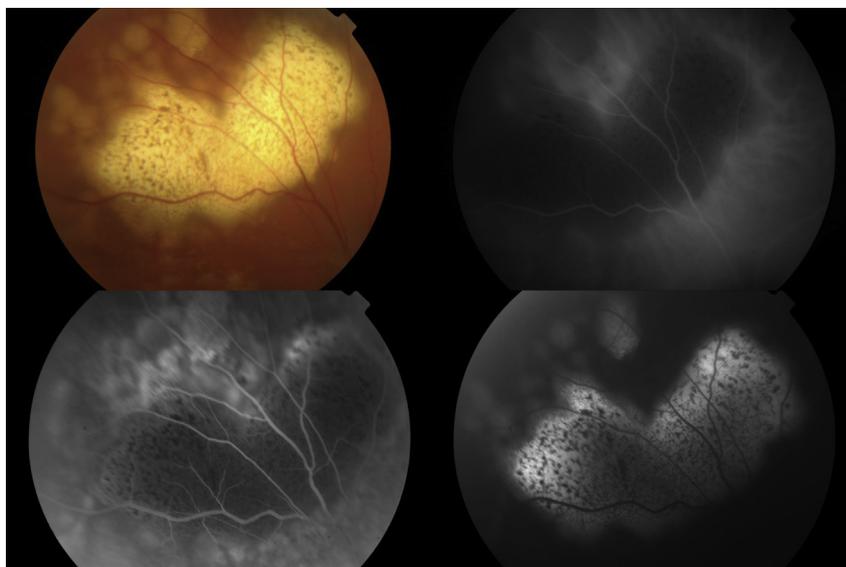
lesions beneath the RPE had a bright hyperautofluorescence appearance, whereas white lesions above the RPE were hypoautofluorescent.<sup>17</sup> This is thought to be the result of lipofuscin in RPE cells.

**7.1.1.3. Optical coherence tomography.** Optical coherence tomography (OCT) findings include nodular hyper-reflective lesions in retinal pigment epithelium layer, reduced foveal thickness compared to uveitis cases, and is useful for confirming the absence of cystoid macular edema.<sup>77,136</sup> Recently, the use of spectral domain OCT has demonstrated lymphomatous subretinal or sub-RPE deposition.<sup>83,199</sup> Further research on the use of OCT to monitor treatment response of such lesions is necessary, but its use is likely to be limited to central, rather than peripheral, fundus involvement.

**7.1.1.4. B mode ultrasound scan.** Ophthalmic ultrasonography can be used to narrow the differential where the posterior segment is difficult to visualize. Abnormal ultrasonographic findings are frequent, although none of the changes are specific for PIOL.<sup>163,196</sup> The most common are vitreous debris, retinal detachment, elevated chorioretinal lesions, and widening of the optic nerve.

#### 7.1.2. Neuroimaging

Magnetic resonance imaging (MRI) with contrast is more sensitive than computed tomography (CT) for detecting lymphomatous lesions in the CNS, but both are limited in evaluating ophthalmic disease.<sup>131</sup> CT and MRI show unifocal or multifocal (in one-third of cases) periventricular, homogeneously enhancing lesions.<sup>16,115</sup> With CT the lesions are isodense or hyperdense, and with MRI, the lesions are hypodense on T1-weighted and hyperdense on T2-weighted images.<sup>37,89</sup> PET/CT has been used to identify CNS lesions as well as



**Fig. 2** – Color fundus photograph of the superonasal lymphomatous infiltrate from **Figure 1** is shown (**top left**), with indocyanine green angiogram (**top right**), highlighting masking of normal choroidal circulation. Fluorescein angiogram (**bottom left**) shows initial masking by the deposit with some perilesional leakage. In the very late frame of the angiogram (**bottom right**), the lesion stains with fluorescein and the retinal pigment epithelial changes and retinal vessels are seen in relief.

ocular activity, both of which take up the 2-[(18)F] fluoro-2-deoxy-D-glucose dye, though the same lesions were identifiable either on MRI or on funduscopy.<sup>148</sup>

## 7.2. Blood testing

Blood tests should be used to rule out conditions in the differential diagnosis, including markers of infectious and non-infectious uveitis.<sup>37</sup> Additionally a complete blood count and human immunodeficiency virus test are useful.<sup>27</sup>

## 7.3. Biopsy

### 7.3.1. Vitreous and retina

Biopsy remains one of the hallmark procedures in diagnosing PIOL.<sup>40,95,123</sup> Tissue biopsy, especially of the vitreous, is performed, especially if PCNSL lesions cannot be found on neuroimaging or when cerebrospinal fluid (CSF) evaluation remains negative. Specimens can be obtained by fine needle vitreous aspiration or pars plana vitrectomy.<sup>40</sup> Multiple biopsies may be required to reach a definite pathological diagnosis.<sup>10,41,112,123,213</sup> The main site of involvement is the sub-RPE space (between RPE and Bruch membrane). The retina, vitreous, and optic nerve head are affected to various degrees.<sup>11,204</sup> The uvea may show a reactive inflammatory cell infiltrate, and uveal biopsies are often nondiagnostic.

Fine needle aspiration of the vitreous is performed with a 21- to 25-gauge needle inserted through the pars plana, although the sample size is small. Generally this is a safe clinical procedure, with a high success rate in differentiating between infectious, inflammatory, and malignant causes of uveitis.<sup>28</sup> An initial diagnosis of intraocular malignancy or infection was confirmed in 40% of patients.<sup>139</sup> Pars plana

vitrectomy has several advantages, including improved vision by clearance of vitreous debris and maximizing the sample size,<sup>40,51,95,145,152,164,216</sup> although extension of the lymphoma through the sclerotomy port to the epibulbar space following vitrectomy may occur.<sup>60</sup>

Vitreous biopsy specimens need to be transported quickly for laboratory analysis.<sup>40,51,212</sup> Lymphoma cells undergo morphological degradation within 60 minutes, but an appropriate preservative may be used if transport time exceeds this.<sup>41,212</sup> The samples should be handled gently to prevent cell degeneration that can make interpretation difficult. In many cases, the paucity of the cells is the result of corticosteroid treatment, which must be discontinued for 2 weeks before the procedure.<sup>212</sup> A negative vitrectomy sample is common, with the lymphoma subsequently diagnosed by brain biopsy when CNS involvement occurs.<sup>18,123</sup> Fixation of the sample in HOPE (HEPES-glutamic acid buffer-mediated Organic solvent Protection Effect) solution may improve the yield and examination requires an experienced cytopathologist.<sup>51,58</sup> Communication with the pathologist before the procedure enables the optimum sample to reach the laboratory, which vary in the techniques they have available.

If subretinal lesions are present, a retinotomy can be performed using the vitreous approach<sup>51,121</sup> or they can also be aspirated.<sup>72,104,135,136,176</sup> Subretinal tumors may consist largely of necrotic tissue, and so specimens are ideally taken from the deeper part of the lesion, near the choriocapillaris, where viable lymphoma cells are most likely to be found.<sup>52</sup> Transcleral biopsy using a partial scleral thickness flap is described.<sup>40,95,121</sup> If the eye is blind and painful or conservative treatment is not possible, a diagnostic enucleation may become necessary.<sup>194</sup> Anterior chamber taps are sometimes

done,<sup>81</sup> though most centers prefer vitreous cytology, as cellular yield is usually better.

### 7.3.2. CSF and brain

A lumbar puncture to obtain CSF is indicated in suspected PCNSL. Up to 25% of patients with identifiable lesions on MRI will have positive CSF cytology.<sup>69,98</sup> If a diagnosis of PCNSL can be made from lymphoma cells found in CSF, and there is simultaneous ocular involvement, then the need for ocular tissue biopsy is less important. Stereotactic brain biopsies can be used in patients with negative CSF findings who have suspicious brain lesions on imaging studies.<sup>18,155</sup>

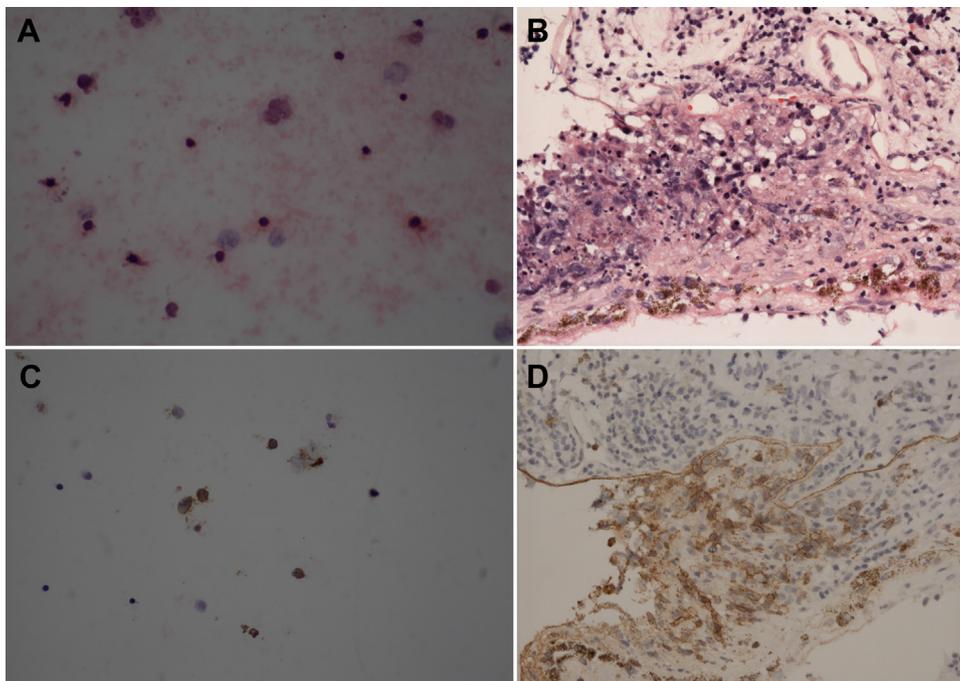
### 7.3.3. Cytological and histological findings

The diagnosis of PIOL requires a multidisciplinary approach. From the pathologist's viewpoint this involves morphological assessment in conjunction with traditional immunocytochemistry and molecular analysis (such as flow cytometry and polymerase chain reaction [PCR] analysis). The techniques used vary with the expertise of the pathologist and the availability of the molecular technique. Pathologists should be made aware of the clinical features, including the cellularity of the vitreous. They can then decide on how to aliquot out the sample. This will usually involve morphological assessment, immunocytochemistry (which can be direct or involve formation into a cell block) and a molecular technique to assess for clonality. Morphologically the typical lymphoma cells are large B-cell lymphoid cells with scanty basophilic cytoplasm, an elevated nucleus:cytoplasm ratio, hypersegmented, round, oval, bean, or clover shaped nuclei with a coarse chromatin pattern and prominent or multiple nucleoli.<sup>2,51,123,137</sup> (Fig. 3). The concordance between clinical

features and pathological diagnosis is as high as 96%.<sup>51</sup> For lymphoma, the positive predictive value of cytologic evaluation was 99–100% and the negative predictive value was 61–81%.<sup>63,210</sup> Sparse number of cells is the main reason for an inconclusive result.<sup>78,123</sup> Vitreous specimens contain many reactive T-lymphocytes, necrotic cells, debris, and fibrin that can also confound the identification of malignant cells.<sup>51</sup>

### 7.3.4. Immunocytochemistry and flow cytometry

The phenotyping of cells by their surface markers is useful for identifying lymphomatous cells, particularly if cytology is scanty.<sup>64,65,112,122,216</sup> Immunocytological techniques use a cell-mounted slide with antibodies directed at specific cell markers.<sup>64,112</sup> Flow cytometry works in a similar fashion, except that 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>65</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>169,221</sup> Both of these methods target monoclonal populations in PIOL, so any contamination by heterogeneous population of B-cells, such as inflammation secondary to malignancy, makes the interpretation of results more difficult.<sup>41</sup> Reactive inflammatory lymphocytes tend to be T-cells and express CD3 and CD5. Hyalocytes (native vitreous cells) that express CD68 may also confound interpretation. In rare cases of T-cell PIOL, immunocytochemistry markers for T-cells such as those mentioned above are positive. Distinction, therefore, from a reactive population by immunocytochemistry is not



**Fig. 3 – Vitreous aspirate (A) and retinotomy specimen (B) showing multiple blue staining lymphoma cells. Lymphoma cells demonstrating positivity of the B-cell marker CD20 in the vitreous (C) and retinotomy (D).**

possible.<sup>62</sup> Thus making the diagnosis of a T-cell PIOL is mainly based on morphology and the demonstration of clonality by molecular techniques.

### 7.3.5. Biochemical and PCR analysis

The production of several interleukins (IL) may assist in differentiating intraocular lymphomas from chronic uveitis. IL-10 was reported to be a growth and differentiation factor for malignant B-lymphocytes.<sup>9,125</sup> IL-10 is elevated in the presence of malignant B-lymphocytes in PIOL/PCSNL, whereas IL-6 or IL-12 is elevated in inflammatory states.<sup>24,38,73,159</sup> IL-10 concentrations above 150 pg/mL in undiluted aqueous or vitreous and of 50 pg/ml or more in diluted aqueous or vitreous specimens were diagnostic of B-cell PIOL.<sup>150</sup> Raised IL-10 in the aqueous was found to have sensitivity of 0.89 and a specificity of 0.93 for the diagnosis of PIOL, and was suggested as a screening test.<sup>26</sup> Moreover, PIOL is reported in some studies to exhibit a high IL-10:IL-6 ratio (>1).<sup>24,38,210,214,219</sup> Wolf et al found the ratio was 74.7% accurate (sensitivity 74%, specificity 75.0%) for 35 patients with PIOL, with the reverse in 64 patients with uveitis.<sup>219</sup> Wang et al reported sensitivity of 88% and specificity of 85% in 80 patients with uveitis or PIOL.<sup>210</sup> The use of the IL-10:IL-6 or IL-10:IL-12 ratios, however, has been controversial as elevation may occur in eyes with non-neoplastic uveitis.<sup>3,4,153</sup> In one report the IL-10:IL-6 or IL-10:IL-12 ratio was elevated in 8 out of 14 vitreous samples from non-neoplastic vitritis eyes.<sup>4</sup> An IL-10:IL-6 ratio <1 has been found in known cases of PIOL.<sup>4,23</sup>

Clonal expansion of B lymphocytes can be assessed using immunoglobulin heavy chain (IgH) gene sequences, particularly in the third complementarity-determining region (CDR3) of the variable region of IgH. The translocation of the bcl-2 proto-oncogene is also involved in the genesis of some lymphoma subtypes<sup>182,208,215</sup> as well as expression of bcl-6 and bcl-10.<sup>208</sup> Studies using PCR on systemic B-cell lymphoma<sup>1</sup> and in PIOL<sup>105,124,182</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>36,182,195,210</sup> Chan et al, in 60 cases of PIOL using this technique, showed rearrangement of the CDR3 of IgH gene in all.<sup>32</sup> In an updated report of 114 cases of B-cell PIOL, all cases had IgH gene rearrangement, but this change was found in only 1 of 86 cases of uveitis.<sup>210</sup> The size of the CDR3 region can also be studied.<sup>97</sup> PCR is not always reliable. In a series of 29 cases, PCR was useful in 17, failed to detect gene rearrangements in 7, and in 5 cases there was insufficient material for PCR.<sup>150</sup> Multiplex primers and semi-nested PCR increase the chances of primer annealing, thus enhancing the detection of monoclonal population.<sup>79,140,198</sup> 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>55,57,141</sup>

IgH gene rearrangements are a marker of clonality, rather than malignancy, and have been found in samples with non-neoplastic uveitis and may be absent in samples diagnosed as PIOL by cytology and flow cytometry.<sup>7</sup> These techniques should be viewed as adjuncts, and more than one approach

improves diagnosis.<sup>30,191</sup> The interpretation of any test should be in the clinical context and involve a multidisciplinary approach.

## 8. Treatment of PIOL

### 8.1. Radiotherapy

Ocular irradiation with prophylactic CNS treatment is used in an attempt to control PIOL, maintain vision, and prevent CNS involvement.<sup>144</sup> In a series of 12 patients with PIOL receiving either chemotherapy alone, radiotherapy alone or a combination, there were no ocular relapses in any patients who had received radiotherapy (30–35 Gy in 15 fractions) during a mean follow-up of 19 months.<sup>15</sup> Localized brain radiotherapy is typically used first line to treat primary CNS lymphoma. If vitreoretinal lymphoma occurs following treatment of CNS lymphoma, whole eye radiotherapy may be added.

High-dose low fractionation CNS radiotherapy can lead to neurotoxicity,<sup>69</sup> including severe depression requiring electroconvulsive therapy.<sup>61</sup> Ocular complications of radiotherapy were dry eye, cataract, and radiation retinopathy.<sup>15</sup>

### 8.2. Chemotherapy

Intravenous methotrexate alone achieved remission of PIOL in 7 out of 9 patients,<sup>13</sup> and intravenous high-dose cytarabine has also been used with variable success.<sup>14,163,190</sup> High dose methotrexate is the most active drug, producing a response rate of up to 72% when used alone and up to 94–100% in combinations.<sup>16,175,193</sup> Osmotic blood brain barrier disruption to increase brain penetration of chemotherapy is associated with non-sight threatening maculopathy.<sup>203</sup>

After high-dose methotrexate-based chemotherapy, cases demonstrating relapse or refractory response treated with high dose chemotherapy with thiotepa, busulfan, and cyclophosphamide, followed by autologous peripheral blood stem cell transplantation, obtained complete remission in 66 out of 79 patients.<sup>185–188</sup> Median survival improved from 28 to 85 months in the high-dose chemotherapy group.<sup>185</sup> Recurrent PIOL with PCNSL has been treated with intrathecal methotrexate and cytarabine.<sup>146</sup> Oral trofosphamide or intravenous iraphosphamide may produce 6–18 months of progression-free survival.<sup>116–119</sup>

### 8.3. Chemoradiation

Chemotherapy after radiation to the eyes and brain in PIOL, initially used as a salvage treatment, may also be a primary treatment.<sup>166,167,220</sup> Intrathecal chemotherapy may be combined with ocular and CNS radiation,<sup>42,197</sup> though systemic chemotherapy is also used. In another radiation treatment study of 15 patients, of which 10 also received chemotherapy, only one had local recurrence.<sup>113</sup> Chemotherapy combined with ocular irradiation resulted in better control of ocular disease than either chemotherapy or non-ocular radiotherapy,<sup>80</sup> and in six PIOL cases receiving ocular radiotherapy and systemic chemotherapy, initial remission was obtained in all, with one patient progressing to PCNSL.<sup>11</sup> Multimodality

treatment results in better disease control, but delayed cognitive neurotoxicity may occur with brain radiation.<sup>155</sup> The British Committee for Standards in Haematology suggests a multimodality approach tailored to disease degree, severity, and performance status of the patient.<sup>143</sup>

#### 8.4. Ocular chemotherapy

##### 8.4.1. Intravitreal methotrexate

Intravitreal chemotherapy with 0.4 mg methotrexate in 0.1 mL achieved local tumor control in relapsed PIOL,<sup>66,67,209</sup> in ocular relapse of PCNSL<sup>127</sup> and as a primary treatment in combination with systemic chemotherapy,<sup>82</sup> intrathecal chemotherapy<sup>184</sup> or sub-Tenon steroid injections.<sup>200</sup> Frenkel and associates<sup>86</sup> reported their 10-year results of using intravitreal methotrexate as a primary treatment for PIOL of B- and T-cell types and some secondary lymphomas. The intravitreal injections were given twice weekly for 4 weeks, weekly for 8 weeks, and then monthly for 9 months—for a total of 25 injections. Remission was reached after a mean of 6.4 injections, with 95% of the eyes needing 13 injections or fewer. Side effects included corneal epitheliopathy, which subsided when the interval between injections increased. Drug resistance may occur with repeated injections.<sup>179</sup> Intravitreal methotrexate has been combined with rituximab and methotrexate based systemic chemotherapy with low-dose (23.4 Gy) brain irradiation in four patients, giving disease-free survival of up to 25 months.<sup>192</sup>

##### 8.4.2. Intravitreal rituximab

Rituximab (1 mg in 0.1 mL), an anti-CD20 monoclonal antibody, is used intravitreally, based on its efficacy in systemic lymphoma.<sup>114,128,129</sup> Initial response was good with clearance of PIOL, but subsequent relapse required intravitreal methotrexate and radiation.<sup>114</sup> Statins have the potential to alter the conformation of the CD20 receptor, which may change the effect of rituximab.<sup>217</sup>

## 9. Prognosis

The reporting of mortality from PIOL in the literature is inconsistent because of diverse 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>2,11,15,27,42,51,71,85,113</sup> Often, diagnosis is delayed.

In PCNSL, median survival of patients treated with radiotherapy alone or chemotherapy plus radiotherapy ranges from 10–16 months, which can be extended to greater than 30 months with methotrexate-based chemotherapy<sup>165</sup> or by ifosfamide or trofosfamide.<sup>118</sup> Grimm and associates<sup>98</sup> had a median progression free survival of 18 months and overall survival of 31 months in 221 patients with PCNSL with intraocular involvement collected from 16 centers in 7 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 versus 35

months—although the group with initial ocular diagnosis was younger.<sup>109</sup>

## 10. Conclusion

When faced with a patient with possible PIOL, there are several diagnostic and therapeutic dilemmas, and opinions differ as to optimal management. It is important to bear a “masquerade syndrome” in mind and have the appropriate index of suspicion based on the clinical signs. Our approach is to ascertain whether there are neurological features on ocular presentation, which would determine the timing of neuroimaging of the brain and spine, usually with MRI. If no neurological features are present, we would advise vitreous and/or subretinal biopsy, in close liaison with the pathologist as to how the specimen is to be handled. Once the diagnosis is confirmed, our regimen is to undertake methotrexate-based systemic chemotherapy with external beam radiotherapy to both eyes and the brain if the patient’s general condition allows. We realize, however, that in some cases only ocular treatment is advised, either with intraocular chemotherapy or radiotherapy. This approach mandates close follow-up for the development of PCNSL. The ophthalmologist and the oncologist jointly monitor response to treatment. This includes systemic examinations with regular MRIs and eye examinations looking for signs of local relapse. If the latter occurs without generalized involvement, then it is our practice to undertake intravitreal methotrexate injections to achieve local tumor control.

In PIOL, there are several contentious areas that merit further research. These include cytologic diagnosis and optimal therapy. New diagnostic modalities are likely to aid quicker diagnosis. The optimal treatment regimen for PIOL has yet to be established and requires a multidisciplinary approach between the ophthalmologist, radiologist, pathologist, and oncologist.<sup>34,158</sup> Even experts in the diagnosis and treatment of PIOL have contrasting views as to the use of systemic versus intravitreal chemotherapy and the role of irradiation.<sup>205</sup> Intravitreal chemotherapy with more than one agent may prove to be useful in ocular disease control. Successful treatment modalities for PCNSL do not automatically translate into successful therapies of PIOL.<sup>45</sup> Given the rarity of this disease, multicenter studies with standardized regimens are more likely to yield useful clinical information. Individualized targeted therapy<sup>33</sup> may evolve from the genetic profile of each PIOL case, as well as advances in drug delivery when new devices for ocular chemotherapy appear.<sup>74</sup>

## 11. Method of literature search

Medline (1950 to end of June 2012) and Embase (1974 to end of June 2012) databases were searched using the search terms *intraocular lymphoma* and *ocular lymphoma*. Removing duplicate articles, excluding articles that clearly related to extraocular lymphoma, and removing foreign language papers provided a total of 221 unique articles in English.

## 12. Disclosure

The authors have no financial or proprietary disclosure in relation to this article.

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