Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/survophthal

Major review

Primary intraocular lymphoma☆

Mandeep S. Sagoo, MB, PhD, MRCOphth, FRCS (Ed)[a,b,c,*], *Hemal Mehta, MA, FRCOphth*[b], *Andrew J. Swampillai, MB, BS*[c], *Victoria M.L. Cohen, MB, BChir, FRCOphth*[b,c], *Sepideh Z. Amin, MBChB, FRCOphth, PhD, FRCPath*[a], *P. Nicholas Plowman, FRCP, FRCR*[d], *Sue Lightman, PhD, FRCP, FRCOphth*[a,b]

[a] *UCL Institute of Ophthalmology, London, UK*
[b] *Moorfields Eye Hospital, London, UK*
[c] *Department of Ophthalmology, St Bartholomew's Hospital, London, UK*
[d] *Department of Oncology, St Bartholomew's Hospital, London, UK*

ARTICLE INFO

Article history:
Received 15 July 2012
Received in revised form 10 December 2013
Accepted 10 December 2013
Available online 31 December 2013

Keywords:
lymphoma
ocular
masquerade
vitreoretinal

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.

* Corresponding author: Dr Mandeep S. Sagoo, MB, PhD, MRCOphth, FRCS (Ed), UCL Institute of Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD.
E-mail address: mandeep.sagoo@moorfields.nhs.uk (M.S. Sagoo).

0039-6257/$ – see front matter
http://dx.doi.org/10.1016/j.survophthal.2013.12.001

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).[6] 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.[171,174] 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;[22,32] although concomitant as well as subsequent intracranial involvement occurs in many cases.[37,54] 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.[22,84,94,142] The secondary type, which typically has different clinical features and prognosis,[32] 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.[207] Systemic T-cell lymphoma with intraocular involvement shares some of the ocular clinical features of typical B-cell PIOL.[132,135]

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[47] and Givner in 1955.[91] This terminology was replaced by the designation ocular reticulum cell sarcoma.[130]

3.2. *Early descriptions*

Klingele 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.[130] 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.[144]

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.[101,102]

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.[101] Most PIOLs are of B-cell origin, and fall within the category of diffuse large B-cell lymphomas.[41,65,216] Isolated PIOLs of T-cell origin occur rarely.[17,25,50,86,92] 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.[46,53,56,59]

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.[85,106] The incidence in the USA has tripled over the past 15 years,[72,106,177] and this rise has been mirrored in Europe.[123] 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.[93,155,172,189] Iatrogenic immunosuppression may also lead to PIOL.[39,49,120,126,173,218] The cause for the increased incidence in immunocompetent patients is unknown.[155] 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.[29]

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

cases in men.[168] 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.[144] 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,[101] but the same association in not documented in PIOL.[160] *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.[181] One suggestion is that an infectious antigen driven B-cell expansion is the primary trigger, which then becomes clonal.[30] Another hypothesis poses haematological transfer of neoplastic cells from nodal and extranodal sites to ocular and central nervous system structures.[21] 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.[35] A disturbance in the factors contributing to the immune privilege of the eye has also been implicated.[31]

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.[21,37,107,133,213]

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

Examination of the posterior segment (Fig. 1) reveals vitritis, which is present in the majority of cases.[2,6,42,163] 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.[2,6,22,27,42,88,110] They can give rise to a characteristic "leopard skin" pigmentation overlying the mass.[88] There may be isolated subretinal lesions,[134] sometimes with associated exudative retinal detachment.[27] Spontaneous resolution may lead to RPE atrophy with subretinal fibrosis.[68] Cystoid macular edema is often absent, in contrast to uveitis cases of similar cellularity,[77] and vision is better than expected from the degree of vitritis. The vitreoretinal form of the disorder can mimic choroiditis or vasculitis.[10,19] Optic nerve infiltration may occur.[90,103] Ocular disease is bilateral in 64–83% of cases, although initially it may seem unilateral.[27,42,107,163] Orbital involvement in PIOL is exceptionally rare.[149,157] 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.[162] The delay between a positive diagnosis and the onset of ocular or neurological symptoms usually varies from 4–40 months,[27,99,107] although rapid progression may occur.[204]

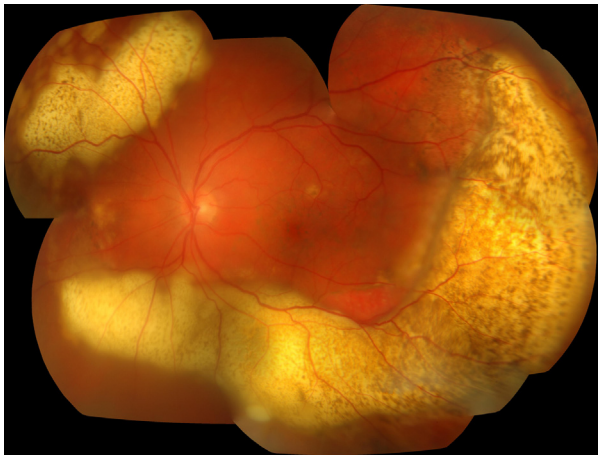

Fig. 1 – Composite color fundus photograph of the left eye of a patient with PIOL. Note the hazy appearance of the fundus due to the presence of vitreous cells, marked yellow subretinal infiltrates with overlying retinal pigment epithelial changes ("leopard spotting") and accumulation of subretinal fluid.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

6.2. CNS features

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

From 13% to 25% of patients with PCNSL have ocular signs on diagnosis.[27,80,104] 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.[2,27,51,85,163] Widespread dissemination of PCNSL can also occur in 7–8% of patients, usually late in the course.[104]

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.[53,56] 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, immunocytchemistry, and polymerase chain reaction,[46] and the subtype is of an extranodal marginal zone or mucosa associated lymphoid tissue lymphoma.[53] 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.[46,56] There is often accompanying extraocular extension.[53,156]

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.[52]

6.4. *Differential diagnosis of PIOL*

As it is a "masquerade syndrome"[10,27,54,76,100,123] (Table 1), the differential diagnosis of PIOL is wide and includes both infectious[5,8,27,44,70,87,96,147,154,161,178] and noninfectious uveitis.[20,27,29,75,90,170,180,206] 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.[12,43,151]

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

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,[27] 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.[201] In another series,[77] 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.[77] Together, the fluorescein and indocyanine green angiographic findings had a positive predictive value of 89% and a negative predictive value of 85%.[77] (Fig. 2).

7.1.1.2. Fundus autofluorescence. In 5 eyes with PIOL the clinically observed brown "leopard spotting" over yellow lesions beneath the RPE had a bright hyperautofluorescence appearance, whereas white lesions above the RPE were hypoautofluorescent.[17] 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.[77,136] Recently, the use of spectral domain OCT has demonstrated lymphomatous subretinal or sub-RPE deposition.[83,199] 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.[163,196] 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.[131] CT and MRI show unifocal or multifocal (in one-third of cases) periventricular, homogenously enhancing lesions.[16,115] With CT the lesions are isodense or hyperdense, and with MRI, the lesions are hypodense on T1-weighted and hyperdense on T2-weighted images.[37,89] PET/CT has been used to identify CNS lesions as well as

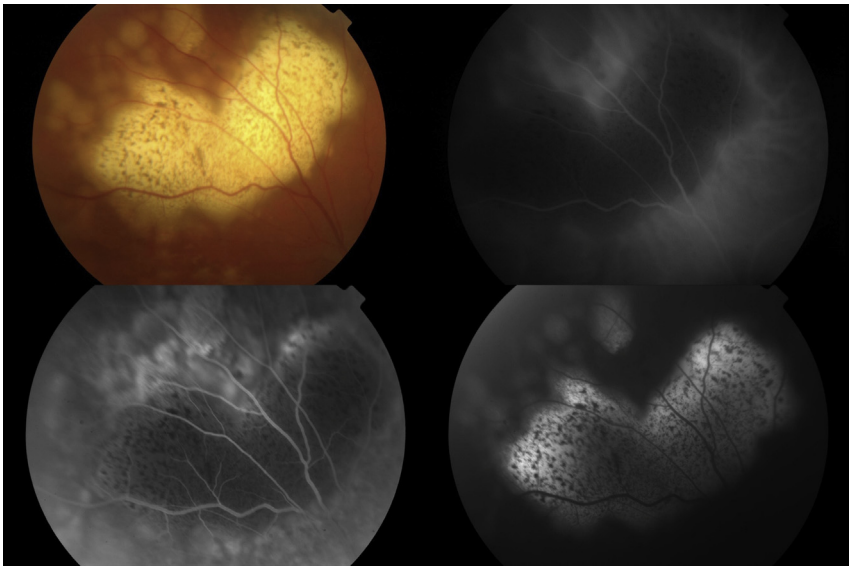

Fig. 2 – Color fundus photograph of the superonasal lymphomatous infiltrate from Figure 1 is shown (*top left*), with indocyanine green angiogram (*top right*), highlighting masking of normal choroidal circulation. Fluorescein angiogram (*bottom left*) shows initial masking by the deposit with some perilesional 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.[148]

7.2. *Blood testing*

Blood tests should be used to rule out conditions in the differential diagnosis, including markers of infectious and noninfectious uveitis.[37] Additionally a complete blood count and human immunodeficiency virus test are useful.[27]

7.3. *Biopsy*

7.3.1. *Vitreous and retina*

Biopsy remains one of the hallmark procedures in diagnosing PIOL.[40,95,123] 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.[40] Multiple biopsies may be required to reach a definite pathological diagnosis.[10,41,112,123,213] 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.[11,204] 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.[28] An initial diagnosis of intraocular malignancy or infection was confirmed in 40% of patients.[139] Pars plana vitrectomy has several advantages, including improved vision by clearance of vitreous debris and maximizing the sample size,[40,51,95,145,152,164,216] although extension of the lymphoma through the sclerotomy port to the epibulbar space following vitrectomy may occur.[60]

Vitreous biopsy specimens need to be transported quickly for laboratory analysis.[40,51,212] Lymphoma cells undergo morphological degradation within 60 minutes, but an appropriate preservative may be used if transport time exceeds this.[41,212] 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.[212] A negative vitrectomy sample is common, with the lymphoma subsequently diagnosed by brain biopsy when CNS involvement occurs.[18,123] 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.[51,58] 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[51,121] or they can also be aspirated.[72,104,135,136,176] 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.[52] Transcleral biopsy using a partial scleral thickness flap is described.[40,95,121] If the eye is blind and painful or conservative treatment is not possible, a diagnostic enucleation may become necessary.[194] Anterior chamber taps are sometimes

done,[81] 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.[69,98] 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.[18,155]

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.[2,51,123,137] (Fig. 3). The concordance between clinical features and pathological diagnosis is as high as 96%.[51] For lymphoma, the positive predictive value of cytologic evaluation was 99–100% and the negative predictive value was 61–81%.[63,210] Sparse number of cells is the main reason for an inconclusive result.[78,123]Vitreous specimens contain many reactive T-lymphocytes, necrotic cells, debris, and fibrin that can also confound the identification of malignant cells.[51]

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.[64,65,112,122,216] Immunocytological techniques use a cell-mounted slide with antibodies directed at specific cell markers.[64,112] 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%,[65] 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.[169,221] 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.[41] 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

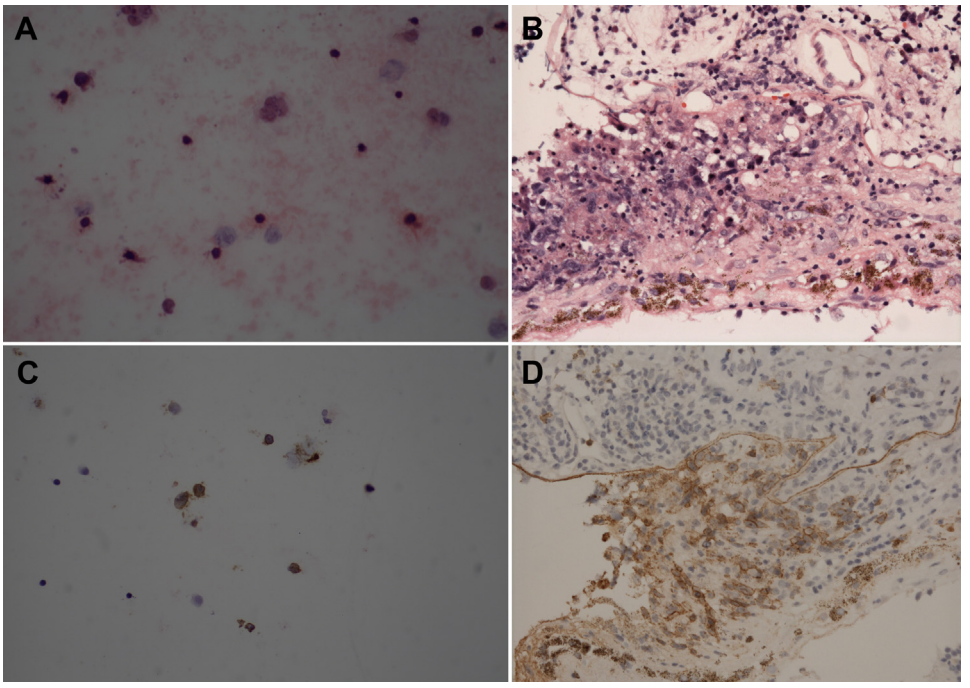

Fig. 3 – Vitreous aspirate (*A*) and retinotomy specimen (*B*) showing multiple blue staining lymphoma cells. Lymphoma cells demonstrating positivity of the B-cell marker CD20 in the vitreous (*C*) and retinotomy (*D*).

possible.[62] 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.[9,125] 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.[24,38,73,159] 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.[150] 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.[26] Moreover, PIOL is reported in some studies to exhibit a high IL-10:IL-6 ratio (>1).[24,38,210,214,219] 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.[219] Wang et al reported sensitivity of 88% and specificity of 85% in 80 patients with uveitis or PIOL.[210] 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.[3,4,153] 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.[4] An IL-10:IL-6 ratio <1 has been found in known cases of PIOL.[4,23]

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[182,208,215] as well as expression of bcl-6 and bcl-10.[208] Studies using PCR on systemic B-cell lymphoma[1] and in PIOL[105,124,182] 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.[36,182,195,210] Chan et al, in 60 cases of PIOL using this technique, showed rearrangement of the CDR3 of IgH gene in all.[32] 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.[210] The size of the CDR3 region can also be studied.[97] 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.[150] Mμltiplex primers and semi-nested PCR increase the chances of primer annealing, thus enhancing the detection of monoclonal population.[79,140,198] 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.[55,57,141]

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.[7] These techniques should be viewed as adjuncts, and more than one approach improves diagnosis.[30,191] 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.[144] 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.[15] 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,[69] including severe depression requiring electroconvulsive therapy.[61] Ocular complications of radiotherapy were dry eye, cataract, and radiation retinopathy.[15]

8.2. *Chemotherapy*

Intravenous methotrexate alone achieved remission of PIOL in 7 out of 9 patients,[13] and intravenous high-dose cytarabine has also been used with variable success.[14,163,190] 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.[16,175,193] Osmotic blood brain barrier disruption to increase brain penetration of chemotherapy is associated with non-sight threatening maculopathy.[203]

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.[185–188] Median survival improved from 28 to 85 months in the high-dose chemotherapy group.[185] Recurrent PIOL with PCNSL has been treated with intrathecal methotrexate and cytarabine.[146] Oral trofosphamide or intravenous iraphosphamide may produce 6–18 months of progression-free survival.[116–119]

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.[166,167,220] Intrathecal chemotherapy may be combined with ocular and CNS radiation,[42,197] 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.[113] Chemotherapy combined with ocular irradiation resulted in better control of ocular disease than either chemotherapy or non-ocular radiotherapy,[80] and in six PIOL cases receiving ocular radiotherapy and systemic chemotherapy, initial remission was obtained in all, with one patient progressing to PCNSL.[11] Multimodality

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

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,[66,67,209] in ocular relapse of PCNSL[127] and as a primary treatment in combination with systemic chemotherapy,[82] intrathecal chemotherapy[184] or sub-Tenon steroid injections.[200] Frenkel and associates[86] 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.[179] 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.[192]

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.[114,128,129] Initial response was good with clearance of PIOL, but subsequent relapse required intravitreal methotrexate and radiation.[114] Statins have the potential to alter the conformation of the CD20 receptor, which may change the effect of rituximab.[217]

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.[2,11,15,27,42,51,71,85,113] 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[165] or by ifosfamide or trofosfamide.[118] Grimm and associates[98] 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.[109]

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.[34,158] 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.[205] 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.[45] Given the rarity of this disease, multicenter studies with standardized regimens are more likely to yield useful clinical information. Individualized targeted therapy[33] may evolve from the genetic profile of each PIOL case, as well as advances in drug delivery when new devices for ocular chemotherapy appear.[74]

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.

REFERENCES

1. Abdel-Reheim FA, Edwards E, Arber DA. Utility of a rapid polymerase chain reaction panel for the detection of molecular changes in B-cell lymphoma. Arch Pathol Lab Med. 1996;120:357–63
2. Akpek EK, Ahmed I, Hochberg FH, et al. Intraocular-central nervous system lymphoma: clinical features, diagnosis, and outcomes. Ophthalmology. 1999;106:1805–10
3. Akpek EK, Foster CS. Primary intraocular lymphoma with a low interleukin 10 to interleukin 6 ratio and heterogeneous IgH gene arrangement. Arch Ophthalmol. 2000;118:731–2
4. Akpek EK, Maca SM, Christen WG, et al. Elevated vitreous interleukin-10 level is not diagnostic of intraocular-central nervous system lymphoma. Ophthalmology. 1999;106:2291–5
5. Androudi S, Brozou CG, Guex-Crosier Y, et al. Ocular tuberculoma mimicking intraocular lymphoma. Ocul Immunol Inflamm. 2009;17:73–5
6. Augsburger JJ, Greatrex KV. Intraocular lymphoma: clinical presentations, differential diagnosis and treatment. Trans PA Acad Ophthalmol Otolaryngol. 1989;41:796–808
7. Baehring JM, Androudi S, Longtine JJ, et al. Analysis of clonal immunoglobulin heavy chain rearrangements in ocular lymphoma. Cancer. 2005;104:591–7
8. Balansard B, Bodaghi B, Cassoux N, et al. Necrotising retinopathies simulating acute retinal necrosis syndrome. Br J Ophthalmol. 2005;89:96–101
9. Banchereau J, Briere F, Liu YJ, et al. Molecular control of B lymphocyte growth and differentiation. Stem Cells. 1994;12:278–88
10. Bardenstein DS. Intraocular lymphoma. Cancer Control. 1998;5:317–25
11. Barr CC, Green WR, Payne JW, et al. Intraocular reticulum-cell sarcoma: clinico-pathologic study of four cases and review of the literature. Surv Ophthalmol. 1975;19:224–39
12. Barton K, Pavesio CE, Towler HM, et al. Uveitis presenting de novo in the elderly. Eye. 1994;8(Pt 3):288–91
13. Batchelor TT, Kolak G, Ciordia R, et al. High-dose methotrexate for intraocular lymphoma. Clin Cancer Res. 2003;9:711–5
14. Baumann MA, Ritch PS, Hande KR, et al. Treatment of intraocular lymphoma with high-dose Ara-C. Cancer. 1986;57:1273–5
15. Berenbom A, Davila RM, Lin HS, et al. Treatment outcomes for primary intraocular lymphoma: implications for external beam radiotherapy. Eye. 2007;21:1198–201
16. Bessell EM, Hoang XK, Ferreri AJM, et al. Primary central nervous system lymphoma: biological aspects and controversies in management. Eur J Cancer. 2007;43:1141–52
17. Bhat PV, Jakobiec FA, Papaliodis G, et al. Primary T-cell lymphoma of the retina and cerebellum: immunophenotypic and gene rearrangement confirmation. Am J Ophthalmol. 2009;148:350–60
18. Blumenkranz MS, Ward T, Murphy S, et al. Applications and limitations of vitreoretinal biopsy techniques in intraocular large cell lymphoma. Retina. 1992;12(3 Suppl):S64–70
19. Brown SM, Jampol LM, Cantrill HL. Intraocular lymphoma presenting as retinal vasculitis. Surv Ophthalmol. 1994;39:133–40
20. Browning DJ, Fraser CM. Primary intraocular lymphoma mimicking multifocal choroiditis and panuveitis. Eye. 2007;21:880–1
21. Buettner H, Bolling JP. Intravitreal large-cell lymphoma. Mayo Clin Proc. 1993;68:1011–5
22. Buggage RR, Chan CC, Nussenblatt RB. Ocular manifestations of central nervous system lymphoma. Curr Opin Oncol. 2001;13:137–42
23. Buggage RR, Velez G, Myers PB, et al. Primary intraocular lymphoma with a low interleukin 10 to interleukin 6 ratio and heterogeneous IgH gene rearrangement. Arch Ophthalmol. 1999;117:1239–42
24. Buggage RR, Whitcup SM, Nussenblatt RB, et al. Using interleukin 10 to interleukin 6 ratio to distinguish primary intraocular lymphoma and uveitis. Invest Ophthalmol Vis Sci. 1999;40:2462–3
25. Calfa CJ, Lossos IS, Ruiz P, et al. Ocular involvement as the initial manifestation of T-cell chronic lymphocytic leukemia. Am J Ophthalmol. 2007;144:326–9
26. Cassoux N, Giron A, Bodaghi B, et al. IL-10 measurement in aqueous humor for screening patients with suspicion of primary intraocular lymphoma. Invest Ophthalmol Vis Sci. 2007;48:3253–9
27. Cassoux N, Merle-Beral H, Leblond V, et al. Ocular and central nervous system lymphoma: clinical features and diagnosis. Ocul Immunol Inflamm. 2000;8:243–50
28. Caya JG, Clowry LJ, Wollenberg NJ, et al. The clinicopathologic significance of vitreous fluid cytology examinations in a series of 38 patients. Diagn Cytopathol. 1985;1:267–71
29. CBTRUS. Statistical report: primary brain tumors in the United States, 1998–2002. Central Brain Tumor Registry of the United States http://www.cbtrus.org/ 2005.
30. Chan CC. Molecular pathology of primary intraocular lymphoma. Trans Am Ophthalmol Soc. 2003;101:275–92
31. Chan CC. Primary intraocular lymphoma: clinical features, diagnosis, and treatment. Clin Lymphoma. 2003;4:30–1
32. Chan CC, Buggage RR, Nussenblatt RB. Intraocular lymphoma. Curr Opin Ophthalmol. 2002;13:411–8
33. Chan CC, Fisson S, Bodaghi B. The future of primary intraocular lymphoma (retinal lymphoma). Ocul Immunol Inflamm. 2009;17:375–9
34. Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. Oncologist. 2011;16:1589–99
35. Chan CC, Shen D, Hackett JJ, et al. Expression of chemokine receptors, CXCR4 and CXCR5, and chemokines, BLC and SDF-1, in the eyes of patients with primary intraocular lymphoma. Ophthalmology. 2003;110:421–6
36. Chan CC, Shen D, Nussenblatt RB, et al. Detection of molecular changes in primary intraocular lymphoma by microdissection and polymerase chain reaction. Diagn Mol Pathol. 1998;7:63–4
37. Chan CC, Wallace DJ. Intraocular lymphoma: update on diagnosis and management. Cancer Control. 2004;11:285–95
38. Chan CC, Whitcup SM, Solomon D, et al. Interleukin-10 in the vitreous of patients with primary intraocular lymphoma. Am J Ophthalmol. 1995;120:671–3
39. Chan SM, Hutnik CM, Heathcote JG, et al. Iris lymphoma in a pediatric cardiac transplant recipient: clinicopathologic findings. Ophthalmology. 2000;107:1479–82
40. Char DH, Kemlitz AE, Miller T. Intraocular biopsy. Ophthalmol Clin N Am. 2005;18:177–85
41. Char DH, Ljung BM, Deschênes J, et al. Intraocular lymphoma: immunological and cytological analysis. Br J Ophthalmol. 1988;72:905–11

42. Char DH, Ljung BM, Miller T, et al. Primary intraocular lymphoma ocular reticulum cell sarcoma diagnosis and management. Ophthalmology. 1988;95:625–30
43. Chatzistefanou K, Markomichelakis NN, Christen W, et al. Characteristics of uveitis presenting for the first time in the elderly. Ophthalmology. 1998;105:347–52
44. Chawla R, Venkatesh P, Garg SP, et al. Cytomegalovirus retinitis in a patient with non-Hodgkin's lymphoma: a diagnostic dilemma. Eur J Ophthalmol. 2005;15:153–7
45. Choi JY, Kafkala C, Foster CS. Primary intraocular lymphoma: A review. Semin Ophthalmol. 2006;21:125–33
46. Cockerham GC, Hidayat AA, Bijwaard KE, et al. Re-evaluation of "reactive lymphoid hyperplasia of the uvea": an immunohistochemical and molecular analysis of 10 cases. Ophthalmology. 2000;107:151–8
47. Cooper EL, Riker JL. Malignant lymphoma of the uveal tract. Am J Ophthalmol. 1951;34:1153–8
48. Corriveau C, Easterbrook M, Payne D. Lymphoma simulating uveitis masquerade syndrome. Can J Ophthalmol. 1986;21:144–9
49. Coskuncan NM, Jabs DA, Dunn JP, et al. The eye in bone marrow transplantation VI Retinal complications. Arch Ophthalmol. 1994;112:372–9
50. Coupland SE, Anastassiou G, Bornfeld N, et al. Primary intraocular lymphoma of T-cell type: report of a case and review of the literature. Graefe's Arch Clin Exp Ophthalmol. 2005;243:189–97
51. Coupland SE, Bechrakis NE, Anastassiou G, et al. Evaluation of vitrectomy specimens and chorioretinal biopsies in the diagnosis of primary intraocular lymphoma in patients with Masquerade syndrome. Graefe's Arch Clin Exp Ophthalmol. 2003;241:860–70
52. Coupland SE, Damato B. Understanding intraocular lymphomas. Clin Experiment Ophthalmol. 2008;36:564–78
53. Coupland SE, Foss HD, Hidayat AA, et al. Extranodal marginal zone B cell lymphomas of the uvea: an analysis of 13 cases. J Pathol. 2002;197:333–40
54. Coupland SE, Heimann H, Bechrakis NE. Primary intraocular lymphoma: a review of the clinical, histopathological and molecular biological features. Graefe's Arch Clin Exp Ophthalmol. 2004;242:901–13
55. Coupland SE, Hummel M, Müller HH, et al. Molecular analysis of immunoglobulin genes in primary intraocular lymphoma. Invest Ophthalmol Vis Sci. 2005;46:3507–14
56. Coupland SE, Joussen A, Anastassiou G, et al. Diagnosis of a primary uveal extranodal marginal zone B-cell lymphoma by chorioretinal biopsy: case report. Graefes Arch Clin Exp Ophthalmol. 2005;243:482–6
57. Coupland SE, Loddenkemper C, Smith JR, et al. Expression of immunoglobulin transcription factors in primary intraocular lymphoma and primary central nervous system lymphoma. Invest Ophthalmol Vis Sci. 2005;46:3957–64
58. Coupland SE, Perez CA, Hummel M, et al. Assessment of HOPE fixation in vitrectomy specimens in patients with chronic bilateral uveitis masquerade syndrome. Graefe's Arch Clin Exp Ophthalmol. 2005;243:847–52
59. Coutinho AB, Muccioli C, Martins MC, et al. Extranodal B-cell lymphoma of the uvea: a case report. Can J Ophthalmol. 2005;40:623–6
60. Cursiefen C, Holbach LM, Lafaut B, et al. Oculocerebral non-Hodgkin's lymphoma with uveal involvement: development of an epibulbar tumor after vitrectomy. Arch Ophthalmol. 2000;118:1437–40
61. Dark F. ECT in a patient receiving prophylactic CNS irradiation for an intraocular lymphoma. Psychosomatics. 1996;37:396–8
62. Davis JL. Diagnosis of intraocular lymphoma. Ocul Immunol Inflamm. 2004;12:7–16
63. Davis JL, Miller DM, Ruiz P. Diagnostic testing of vitrectomy specimens. Am J Ophthalmol. 2005;140:822–9
64. Davis JL, Solomon D, Nussenblatt RB, et al. Immunocytochemical staining of vitreous cells Indications, techniques, and results. Ophthalmology. 1992;99:250–6
65. Davis JL, Viciana AL, Ruiz P. Diagnosis of intraocular lymphoma by flow cytometry. Am J Ophthalmol. 1997;124:362–72
66. de Smet MD, Stark-Vancs V, Kohler DR, et al. Intraocular levels of methotrexate after intravenous administration. Am J Ophthalmol. 1996;121:442–4
67. de Smet MD, Vancs VS, Kohler D, et al. Intravitreal chemotherapy for the treatment of recurrent intraocular lymphoma. Br J Ophthalmol. 1999;83:448–51
68. Dean JM, Novak MA, Chan CC, et al. Tumor detachments of the retinal pigment epithelium in ocular/central nervous system lymphoma. Retina. 1996;16:47–56
69. DeAngelis LM. Primary central nervous system lymphomas. Curr Treat Options Oncol. 2001;2:309–18
70. Derzko DLA, Berger AR, Berinstein NL. Cytomegalovirus retinitis and low-grade non-Hodgkin's lymphoma: case report and review of the literature. Am J Hematol. 1998;57:228–32
71. Dunleavy K, Wilson WH. Primary intraocular lymphoma: current and future perspectives. Leuk Lymphoma. 2006;47:1726–7
72. Eby NL, Grufferman S, Flannelly CM, et al. Increasing incidence of primary brain lymphoma in the US. Cancer. 1988;62:2461–5
73. El-Shabrawi Y, Livir-Rallatos C, Christen W, et al. High levels of interleukin-12 in the aqueous humor and vitreous of patients with uveitis. Ophthalmology. 1998;105:1659–63
74. Eljarrat BE, Domb AJ, Orucov F, et al. Methotrexate delivery to the eye using transscleral hydrogel iontophoresis. Curr Eye Res. 2007;32:639–46
75. Fahim DK, Bucher R, Johnson MW. The elusive nature of primary intraocular lymphoma. J Neuroophthalmol. 2005;25:33–6
76. Faia LJ, Chan CC. Primary intraocular lymphoma. Arch Pathol Lab Med. 2009;133:1228–32
77. Fardeau C, Lee CP, Merle-Beral H, et al. Retinal fluorescein, indocyanine green angiography, and optic coherence tomography in non-Hodgkin primary intraocular lymphoma. Am J Ophthalmol. 2009;147:886–94, 894.e881.
78. Farkas T, Harbour JW, Dávila RM. Cytologic diagnosis of intraocular lymphoma in vitreous aspirates. Acta Cytol. 2004;48:487–91
79. Feilmeier MR, Lossos IS, Malumbres R, et al. Successful use of semi-nested PCR for the diagnosis of primary intraocular lymphoma. Leuk Lymphoma. 2008;49:1–4
80. Ferreri AJM, Blay JY, Reni M, et al. Relevance of intraocular involvement in the management of primary central nervous system lymphomas. Ann Oncol. 2002;13:531–8
81. Finger PT, Papp C, Latkany P, et al. Anterior chamber paracentesis cytology cytospin technique for the diagnosis of intraocular lymphoma. Br J Ophthalmol. 2006;90:690–2
82. Fishburne BC, Wilson DJ, Rosenbaum JT, et al. Intravitreal methotrexate as an adjunctive treatment of intraocular lymphoma. Arch Ophthalmol. 1997;115:1152–6
83. Forooghian F, Merkur AB, White VA, et al. High-definition optical coherence tomography features of primary vitreoretinal lymphoma. Ophthalmic Surg Lasers Imaging. 2011;42:e97–9, Online.
84. Fredrick DR, Char DH, Ljung BM, et al. Solitary intraocular lymphoma as an initial presentation of widespread disease. Arch Ophthalmol. 1989;107:395–7

85. Freeman LN, Schachat AP, Knox DL, et al. Clinical features, laboratory investigations, and survival in ocular reticulum cell sarcoma. Ophthalmology. 1987;94:1631–9
86. Frenkel S, Hendler K, Siegal T, et al. Intravitreal methotrexate for treating vitreoretinal lymphoma: 10 years of experience. Br J Ophthalmol. 2008;92:383–8
87. Gallagher MJ, Cervantes CRC, Bhat P, et al. Primary intraocular lymphoma: Another great masquerader. Eur J Ophthalmol. 2008;18:567–71
88. Gass JD, Sever RJ, Grizzard WS, et al. Multifocal pigment epithelial detachments by reticulum cell sarcoma. A characteristic funduscopic picture. Retina. 1984;4:135–43
89. Gerber S, Reux I, Cassoux N, et al. Intra-ocular lymphoma with and without CNS involvement: Diagnosis and follow-up. A report of 15 cases studied by MR. Neuroradiol J. 1998;11:161–70
90. Gill MK, Jampol LM. Variations in the presentation of primary intraocular lymphoma: case reports and a review. Surv Ophthalmol. 2001;45:463–71
91. Givner I. Malignant lymphoma with ocular involvement; a clinico-pathologic report. Am J Ophthalmol. 1955;39:29–32
92. Goeminne JC, Brouillard A, Jaumain P, et al. Bilateral granulomatous panuveitis as initial presentation of diffuse systemic T cell lymphoma. Ophthalmologica. 1999;213:323–6
93. Goldberg DE, Smithen LM, Angelilli A, et al. HIV-associated retinopathy in the HAART era. Retina. 2005;25:633–49
94. Gombos DS, O'Brien JM. Management of systemic malignancies metastatic to the eye and orbit. Ophthalmol Clin N Am. 1999;12:225–34
95. Gonzales JA, Chan CC. Biopsy techniques and yields in diagnosing primary intraocular lymphoma. Int Ophthalmol. 2007;27:241–50
96. Gooi P, Farmer J, Hurley B, et al. Cytomegalovirus retinitis mimicking intraocular lymphoma. Clin Ophthalmol. 2008;2:969–71
97. Gorochov G, Parizot C, Bodaghi B, et al. Characterization of vitreous B-cell infiltrates in patients with primary ocular lymphoma, using CDR3 size polymorphism analysis of antibody transcripts. Invest Ophthalmol Vis Sci. 2003;44:5235–41
98. Grimm SA, McCannel CA, Omuro AM, et al. Primary CNS lymphoma with intraocular involvement: International PCNSL Collaborative Group Report. Neurology. 2008;71:1355–60
99. Grimm SA, Pulido JS, Jahnke K, et al. Primary intraocular lymphoma: an International Primary Central Nervous System Lymphoma Collaborative Group Report. Ann Oncol. 2007;18:1851–5
100. Gündüz K, Pulido JS, McCannel CA, et al. Ocular manifestations and treatment of central nervous system lymphomas. Neurosurg Focus. 2006;21:E9
101. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting—Airlie House, Virginia, November 1997. J Clin Oncol. 1999;17:3835–49
102. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood. 1994;84:1361–92
103. Hedayatfar A, Phaik Chee S. Presumptive primary intraocular lymphoma presented as an intraocular mass involving the optic nerve head. J Ophthalmic Inflamm Infect. 2012;2:49–51
104. Herrlinger U. Primary CNS lymphoma: findings outside the brain. J Neurooncol. 1999;43:227–30
105. Higashide T, Takahira M, Okumura H, et al. Bilaterally identical monoclonality in a case of primary intraocular lymphoma. Am J Ophthalmol. 2004;138:306–8
106. Hochberg FH, Miller DC. Primary central nervous system lymphoma. J Neurosurg. 1988;68:835–53
107. Hoffman PM, McKelvie P, Hall AJ, et al. Intraocular lymphoma: a series of 14 patients with clinicopathological features and treatment outcomes. Eye. 2003;17:513–21
108. Hon C, Au WY, Shek TW. Intraocular lymphoma as a masquerade syndrome complicating cerebral lymphoma of the corpus callosum. Ann Hematol. 2005;84:203–4
109. Hormigo A, Abrey L, Heinemann MH, et al. Ocular presentation of primary central nervous system lymphoma: diagnosis and treatment. Br J Haematol. 2004;126:202–8
110. Hormigo A, DeAngelis LM. Primary ocular lymphoma: clinical features, diagnosis, and treatment. Clin Lymphoma. 2003;4:22–9
111. Hykin PG, MacSweeney JE, Gartry D, Graham E. Primary intraocular lymphoma with lymphomatous meningitis. J R Soc Med. 1990;83:51–2
112. Intzedy L, Teoh SCB, Hogan A, et al. Cytopathological analysis of vitreous in intraocular lymphoma. Eye. 2008;22:289–93
113. Isobe K, Ejima Y, Tokumaru S, et al. Treatment of primary intraocular lymphoma with radiation therapy: a multi-institutional survey in Japan. Leuk Lymphoma. 2006;47:1800–5
114. Itty S, Olson JH, O'Connell DJ, et al. Treatment of primary intraocular lymphoma (PIOL) has involved systemic, intravitreal or intrathecal chemotherapy and/or radiotherapy. Retina. 2009;29:415–6
115. Jack CR Jr, O'Neill BP, Banks PM, et al. Central nervous system lymphoma: histologic types and CT appearance. Radiology. 1988;167:211–5
116. Jahnke K, Bechrakis NE, Coupland SE, et al. Treatment of primary intraocular lymphoma with oral trofosfamide: report of two cases and review of the literature. Graefe's Arch Clin Exp Ophthalmol. 2004;242:771–6
117. Jahnke K, Korfel A, Komm J, et al. Intraocular lymphoma 2000-2005: results of a retrospective multicentre trial. Graefe's Arch Clin Exp Ophthalmol. 2006;244:663–9
118. Jahnke K, Thiel E, Bechrakis NE, et al. Ifosfamide or trofosfamide in patients with intraocular lymphoma. J Neurooncol. 2009;93:213–7
119. Jahnke K, Wagner T, Bechrakis NE, et al. Pharmacokinetics and efficacy of ifosfamide or trofosfamide in patients with intraocular lymphoma. Ann Oncol. 2005;16:1974–8
120. Johnson BL. Intraocular and central nervous system lymphoma in a cardiac transplant recipient. Ophthalmology. 1992;99:987–92
121. Johnston RL, Tufail A, Lightman S, et al. Retinal and choroidal biopsies are helpful in unclear uveitis of suspected infectious or malignant origin. Ophthalmology. 2004;111:522–8
122. Karikehalli S, Nazeer T, Lee CY. Intraocular large B-cell lymphoma A case report. Acta Cytol. 2004;48:207–10
123. Karma A, von WEO, Tommila PV, et al. Primary intraocular lymphoma: improving the diagnostic procedure. Ophthalmology. 2007;114:1372–7
124. Katai N, Kuroiwa S, Fujimori K, et al. Diagnosis of intraocular lymphoma by polymerase chain reaction. Graefe's Arch Clin Exp Ophthalmol. 1997;235:431–6
125. Khatri VP, Caligiuri MA. A review of the association between interleukin-10 and human B-cell malignancies. Cancer Immunol Immunother. 1998;46:239–44
126. Kheterpal S, Kirkby GR, Neuberger JM, et al. Intraocular lymphoma after liver transplantation. Am J Ophthalmol. 1993;116:507–8

127. Kim E, Kim C, Lee J, et al. A case of primary intraocular lymphoma treated by intravitreal methotrexate. Korean J Ophthalmol. 2009;23:210–4
128. Kim H, Csaky KG, Chan CC, et al. The pharmacokinetics of rituximab following an intravitreal injection. Exp Eye Res. 2006;82:760–6
129. Kitzmann AS, Pulido JS, Mohney BG, et al. Intraocular use of rituximab. Eye. 2007;21:1524–7
130. Klingele TG, Hogan MJ. Ocular reticulum cell sarcoma. Am J Ophthalmol. 1975;79:39–47
131. Küker W, Herrlinger U, Grönewäller E, et al. Ocular manifestation of primary nervous system lymphoma: what can be expected from imaging? J Neurol. 2002;249:1713–6
132. Kumar SR, Gill PS, Wagner DG, et al. Human T-cell lymphotropic virus type I-associated retinal lymphoma A clinicopathologic report. Arch Ophthalmol. 1994;112:954–9
133. Levy CGA, Chan CC, Nussenblatt RB. Diagnosis and management of primary intraocular lymphoma. Hematol Oncol Clin North Am. 2005;19:739–49
134. Levy-Clarke GA, Byrnes GA, Buggage RR, et al. Primary intraocular lymphoma diagnosed by fine needle aspiration biopsy of a subretinal lesion. Retina. 2001;21:281–4
135. Levy-Clarke GA, Greenman D, Sieving PC, et al. Ophthalmic manifestations, cytology, immunohistochemistry, and molecular analysis of intraocular metastatic T-cell lymphoma: report of a case and review of the literature. Surv Ophthalmol. 2008;53:285–95
136. Liang F, Barale PO, Hoang Xuan K, et al. Subretinal lymphomatous infiltration in primary intraocular lymphoma revealed by optical coherence tomography. Graefes Arch Clin Exp Ophthalmol. 2011;249:1425–7
137. Ljung BM, Char D, Miller TR, et al. Intraocular lymphoma: cytologic diagnosis and the role of immunologic markers. Acta Cytol. 1988;32:840–7
138. Lobo A, Larkin G, Clark BJ, et al. Pseudo-hypopyon as the presenting feature in B-cell and T-cell intraocular lymphoma. Clin Experiment Ophthalmol. 2003;31:155–8
139. Lobo A, Lightman S. Vitreous aspiration needle tap in the diagnosis of intraocular inflammation. Ophthalmology. 2003;110:595–9
140. Lobo A, Okhravi N, Adamson P, et al. Protocol for the use of polymerase chain reaction in the detection of intraocular large B-cell lymphoma in ocular samples. J Mol Diagn. 2007;9:113–21
141. Malumbres R, Davis J, Ruiz P, et al. Somatically mutated immunoglobulin IGHV@ genes without intraclonal heterogeneity indicate a postgerminal centre origin of primary intraocular diffuse large B-cell lymphomas. Br J Haematol. 2007;138:749–55
142. Marcus HC. Malignant lymphoma of the uveal tract. Arch Ophthalmol. 1963;69:251–3
143. Marcus R, Hodson D, Coupland S, et al. British Committee for Standards in Haematology. Guidelines on the diagnosis and management of adult patients with primary CNS lymphoma (PCNSL) and primary intra-ocular lymphoma (PIOL). http://www.bcshguidelines.com/documents/PCNSL__bcsh_2007.pdf, accessed June 2012.
144. Margolis L, Fraser R, Lichter A, et al. The role of radiation therapy in the management of ocular reticulum cell sarcoma. Cancer. 1980;45:688–92
145. Margolis R. Diagnostic vitrectomy for the diagnosis and management of posterior uveitis of unknown etiology. Curr Opin Ophthalmol. 2008;19:218–24
146. Mason JO, Fischer DH. Intrathecal chemotherapy for recurrent central nervous system intraocular lymphoma. Ophthalmology. 2003;110:1241–4
147. Matsuo K, Nakatuka K, Matsuura T, et al. Primary intraocular lymphoma mimicking late postoperative endophthalmitis. Ophthalmologica. 1995;209:331–5
148. Matsuo T, Ichimura K, Ichikawa T, et al. Positron emission tomography/computed tomography after immunocytochemical and clonal diagnosis of intraocular lymphoma with vitrectomy cell blocks. J Clin Exp Hematop. 2009;49:77–87
149. Matzkin DC, Slamovits TL, Rosenbaum PS. Simultaneous intraocular and orbital non-Hodgkin lymphoma in the acquired immune deficiency syndrome. Ophthalmology. 1994;101:850–5
150. Merle-Béral H, Davi F, Cassoux N, et al. Biological diagnosis of primary intraocular lymphoma. Br J Haematol. 2004;124:469–73
151. Mochizuki M, Singh AD. Epidemiology and clinical features of intraocular lymphoma. Ocul Immunol Inflamm. 2009;17:69–72
152. Mruthyunjaya P, Jumper JM, McCallum R, et al. Diagnostic yield of vitrectomy in eyes with suspected posterior segment infection or malignancy. Ophthalmology. 2002;109:1123–9
153. Muhaya M, Calder VL, Towler HM, et al. Characterization of phenotype and cytokine profiles of T cell lines derived from vitreous humour in ocular inflammation in man. Clin Exp Immunol. 1999;116:410–4
154. Nasir MA, Jaffe GJ. Cytomegalovirus retinitis associated with Hodgkin's disease. Retina. 1996;16:324–7
155. Nasir S, DeAngelis LM. Update on the management of primary CNS lymphoma. Oncology. 2000;14:228–34, discussion 237–242, 244.
156. Neudorfer M, Kessler A, Anteby I, et al. Co-existence of intraocular and orbital lymphoma. Acta Ophthalmol Scand. 2004;82:754–61
157. Noda S, Hayasaka S, Setogawa T. Intraocular lymphoma invades the optic nerve and orbit. Ann Ophthalmol. 1993;25:30–4
158. Nussenblatt RB, Chan CC, Wilson WH, et al. International Central Nervous System and Ocular Lymphoma Workshop: recommendations for the future. Ocul Immunol Inflamm. 2006;14:139–44
159. Ohta K, Sano K, Imai H, et al. Cytokine and molecular analyses of intraocular lymphoma. Ocul Immunol Inflamm. 2009;17:142–7
160. Ongkosuwito JV, Van der Lelij A, Bruinenberg M, et al. Increased presence of Epstein-Barr virus DNA in ocular fluid samples from HIV negative immunocompromised patients with uveitis. Br J Ophthalmol. 1998;82:245–51
161. Ormerod LD, Puklin JE. AIDS-associated intraocular lymphoma causing primary retinal vasculitis. Ocul Immunol Inflamm. 1997;5:271–8
162. Parikh AH, Khan SH, Wright JD Jr, et al. Systemic non-Hodgkin's lymphoma simulating primary intraocular lymphoma. Am J Ophthalmol. 2005;139:573–4
163. Peterson K, Gordon KB, Heinemann MH, et al. The clinical spectrum of ocular lymphoma. Cancer. 1993;72:843–9
164. Peyman GA. A pneumovitrector for the diagnostic biopsy of the vitreous. Ophthalmic Surg Lasers. 1996;27:246–7
165. Plotkin SR, Batchelor TT. Primary nervous-system lymphoma. Lancet Oncol. 2001;2:354–5
166. Plowman PN, Montefiore DS, Lightman S. Multiagent chemotherapy in the salvage cure of ocular lymphoma relapsing after radiotherapy. Clin Oncol. 1993;5:315–6
167. Plowman PN, Taylor A, Jackson ASN, et al. Optimal therapy of primary ocular lymphoma. Clin Oncol. 2002;14:521
168. Qualman SJ, Mendelsohn G, Mann RB, et al. Intraocular lymphomas: natural history based on a clinicopathologic study of eight cases and review of the literature. Cancer. 1983;52:878–86

169. Raparia K, Chang CC, Chevez-Barrios P. Intraocular lymphoma: diagnostic approach and immunophenotypic findings in vitrectomy specimens. Arch Pathol Lab Med. 2009;133:1233–7
170. Rattray KM, Cole MD, Smith SR. Systemic non-Hodgkin's lymphoma presenting as a serpiginous choroidopathy: report of a case and review of the literature. Eye. 2000;14:706–10
171. Read RW, Zamir E, Rao NA. Neoplastic masquerade syndromes. Surv Ophthalmol. 2002;47:81–124
172. Rivero ME, Kuppermann BD, Wiley CA, et al. Acquired immunodeficiency syndrome-related intraocular B-cell lymphoma. Arch Ophthalmol. 1999;117:616–22
173. Rizkalla K, Rodrigues S, Proulx A, et al. Primary intraocular lymphoma arising during methotrexate treatment of temporal arteritis. Can J Ophthalmol. 2005;40:585–92
174. Rothova A, Ooijman F, Kerkhoff F, et al. Uveitis masquerade syndromes. Ophthalmology. 2001;108:386–99
175. Sandor V, Stark VV, Pearson D, et al. Phase II trial of chemotherapy alone for primary CNS and intraocular lymphoma. J Clin Oncol. 1998;16:3000–6
176. Sarafzadeh S, Correa ZM, Dhamija A, et al. Intraocular lymphoma diagnosed by fine-needle aspiration biopsy. Acta Ophthalmol. 2009;86:705–10
177. Schabet M. Epidemiology of primary CNS lymphoma. J Neurooncol. 1999;43:199–201
178. Sen HN, Bodaghi B, Hoang PL, et al. Primary intraocular lymphoma: diagnosis and differential diagnosis. Ocul Immunol Inflamm. 2009;17:133–41
179. Sen HN, Chan CC, Byrnes G, et al. Intravitreal methotrexate resistance in a patient with primary intraocular lymphoma. Ocul Immunol Inflamm. 2008;16:29–33
180. Shah GK, Kleiner RC, Augsburger JJ, et al. Primary intraocular lymphoma seen with transient white fundus lesions simulating the multiple evanescent white dot syndrome. Arch Ophthalmol. 2001;119:617–20
181. Shen DF, Herbort CP, Tuaillon N, et al. Detection of Toxoplasma gondii DNA in primary intraocular B-cell lymphoma. Mod Pathol. 2001;14:995–9
182. Shen DF, Zhuang Z, LeHoang P, et al. Utility of microdissection and polymerase chain reaction for the detection of immunoglobulin gene rearrangement and translocation in primary intraocular lymphoma. Ophthalmology. 1998;105:1664–9
183. Sobrin L, Dubovy SR, Davis JL, et al. Isolated, bilateral intraocular lymphoma in a 15-year-old girl. Retina. 2005;25:370–3
184. Sou R, Ohguro N, Maeda T, et al. Treatment of primary intraocular lymphoma with intravitreal methotrexate. Jpn J Ophthalmol. 2008;52:167–74
185. Soussain C, Choquet S, Fourme E, et al. Intensive chemotherapy with thiotepa, busulfan and cyclophosphamide and hematopoietic stem cell rescue in relapsed or refractory primary central nervous system lymphoma and intraocular lymphoma: a retrospective study of 79 cases. Haematologica. 2012;97:1751–6
186. Soussain C, Hoang XK, Taillandier L, et al. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire. J Clin Oncol. 2008;26:2512–8
187. Soussain C, Merle BH, Reux I, et al. A single-center study of 11 patients with intraocular lymphoma treated with conventional chemotherapy followed by high-dose chemotherapy and autologous bone marrow transplantation in 5 cases. Leuk Lymphoma. 1996;23:339–45
188. Soussain C, Suzan F, Hoang XK, et al. Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. J Clin Oncol. 2001;19:742–9
189. Stanton CA, Sloan B 3rd, Slusher MM, Greven CM. Acquired immunodeficiency syndrome-related primary intraocular lymphoma. Arch Ophthalmol. 1992;110:1614–7
190. Strauchen JA, Dalton J, Friedman AH. Chemotherapy in the management of intraocular lymphoma. Cancer. 1989;63:1918–21
191. Sugita S, Takase H, Sugamoto Y, et al. Diagnosis of intraocular lymphoma by polymerase chain reaction analysis and cytokine profiling of the vitreous fluid. Jpn J Ophthalmol. 2009;53:209–14
192. Taoka K, Yamamoto G, Kaburaki T, et al. Treatment of primary intraocular lymphoma with rituximab, high dose methotrexate, procarbazine, and vincristine chemotherapy, reduced whole-brain radiotherapy, and local ocular therapy. Br J Haematol. 2012;157:252–4
193. Tempescul A, Pradier O, Marianowski-Cochard C, et al. Combined therapy associating systemic platinum-based chemotherapy and local radiotherapy into the treatment of primary intraocular lymphoma. Ann Hematol. 2011;90:1117–8
194. Trudeau M, Shepherd FA, Blackstein ME, et al. Intraocular lymphoma: report of three cases and review of the literature. Am J Clin Oncol. 1988;11:126–30
195. Tuaillon N, Chan CC. Molecular analysis of primary central nervous system and primary intraocular lymphomas. Curr Mol Med. 2001;1:259–72
196. Ursea R, Heinemann MH, Silverman RH, et al. Ophthalmic, ultrasonographic findings in primary central nervous system lymphoma with ocular involvement. Retina. 1997;17:118–23
197. Valluri S, Moorthy RS, Khan A, et al. Combination treatment of intraocular lymphoma. Retina. 1995;15:125–9
198. van Dongen JJ, Langerak AW, Bruggemann M, et al. Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 Concerted Action BMH4-CT98-3936. Leukemia. 2003;17:2257–317
199. Vasconcelos-Santos DV, De Puy ESGH, de Faria BB, et al. Subretinal pigment epithelial infiltrates in primary vitreoretinal lymphoma. J Ophthalmic Inflamm Infect. 2011;1:171
200. Velez G, Boldt HC, Whitcup SM, et al. Local methotrexate and dexamethasone phosphate for the treatment of recurrent primary intraocular lymphoma. Ophthalmic Surg Lasers. 2002;33:329–33
201. Velez G, Chan CC, Csaky KG. Fluorescein angiographic findings in primary intraocular lymphoma. Retina. 2002;22:37–43
202. Velez G, de Smet MD, Whitcup SM, et al. Iris involvement in primary intraocular lymphoma: report of two cases and review of the literature. Surv Ophthalmol. 2000;44:518–26
203. Vicuna KJ, Frenkel S, Siegal T, et al. Maculopathy in patients with primary CNS lymphoma treated with chemotherapy in conjunction with blood-brain barrier disruption. Br J Ophthalmol. 2008;92:231–5
204. Vogel MH, Font RL, Zimmerman LE, et al. Reticulum cell sarcoma of the retina and uvea. Report of six cases and review of the literature. Am J Ophthalmol. 1968;66:205–15
205. Wakefield D, Zierhut M. Intraocular lymphoma: more questions than answers. Ocul Immunol Inflamm. 2009;17:6–10
206. Walker J, Ober RR, Khan A, et al. Intraocular lymphoma developing in a patient with Vogt-Koyanagi-Harada syndrome. Int Ophthalmol. 1993;17:331–6

207. Wallace DJ, Altemare CR, Shen DF, et al. Primary testicular and intraocular lymphomas: two case reports and a review of the literature. Surv Ophthalmol. 2006;51:41–50
208. Wallace DJ, Shen D, Reed GF, et al. Detection of the bcl-2 t14; 18 translocation and proto-oncogene expression in primary intraocular lymphoma. Invest Ophthalmol Vis Sci. 2006;47:2750–6
209. Wang JK, Yang CM, Lin CP, et al. An Asian patient with intraocular lymphoma treated by intravitreal methotrexate. Jpn J Ophthalmol. 2006;50:474–8
210. Wang Y, Shen D, Wang VM, et al. Molecular biomarkers for the diagnosis of primary vitreoretinal lymphoma. Int J Mol Sci. 2011;12:5684–97
211. Wender A, Adar A, Maor E, et al. Primary B-cell lymphoma of the eyes and brain in a 3-year-old boy. Arch Ophthalmol. 1994;112:450–1
212. Whitcup SM, Chan CC, Buggage RR, et al. Improving the diagnostic yield of vitrectomy for intraocular lymphoma. Arch Ophthalmol. 2000;118:446
213. Whitcup SM, de Smet MD, Rubin BI, et al. Intraocular lymphoma Clinical and histopathologic diagnosis. Ophthalmology. 1993;100:1399–406
214. Whitcup SM, Stark VV, Wittes RE, et al. Association of interleukin 10 in the vitreous and cerebrospinal fluid and primary central nervous system lymphoma. Arch Ophthalmol. 1997;115:1157–60
215. White VA, Gascoyne RD, Paton KE. Use of the polymerase chain reaction to detect B- and T-cell gene rearrangements in vitreous specimens from patients with intraocular lymphoma. Arch Ophthalmol. 1999;117:761–5
216. Wilson DJ, Braziel R, Rosenbaum JT. Intraocular lymphoma Immunopathologic analysis of vitreous biopsy specimens. Arch Ophthalmol. 1992;110:1455–8
217. Winiarska M, Bil J, Wilczek E, et al. Statins impair antitumor effects of rituximab by inducing conformational changes of CD20. PLoS Med. 2008;5:e64
218. Woei AJFJ, Kersting S, Bollemeijer JG. Primary intraocular lymphoma in a patient with systemic lupus erythematosus. Ann Hematol. 2012;91:1821–2
219. Wolf LA, Reed GF, Buggage RR, et al. Vitreous cytokine levels. Ophthalmology. 2003;110:1671–2
220. Woolf DK, Ahmed M, Plowman PN. Primary lymphoma of the ocular adnexa (orbital lymphoma) and primary intraocular lymphoma. Clin Oncol (R Coll Radiol). 2012;24:339–44
221. Zaldivar RA, Martin DF, Holden JT, et al. Primary intraocular lymphoma: clinical, cytologic, and flow cytometric analysis. Ophthalmology. 2004;111:1762–7