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Primary intraocular lymphoma: a review of the clinical, histopathological and molecular biological features

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Abstract *Introduction:* Primary intraocular lymphoma (PIOL) is a rare non-Hodgkin lymphoma which arises in the retina or the vitreous. It can occur either together with or independently of primary cerebral nervous system lymphoma (PCNSL); the incidence of the latter has significantly increased over the past three decades. PIOL remains one of the most difficult diagnoses to establish, particularly due to its ability to mimic other diseases in the eye and to the limited material which is often available for examination. *Methods:* The article reviews the clinical, histopathological, molecular biological and biochemical approaches to the diagnosis of PIOL. The differential diagnoses, including other lymphomatous manifestations in the eye, e.g. primary uveal lymphoma, as well as non-neoplastic uveal diseases are addressed. Furthermore, the treatment strategies for PIOL are summarised. *Results:* Diagnostic progress has been made in various fields, including flow cytometry and immunocytology, cytokine analysis, and as well as molecular biological analysis of the immunoglobulin heavy and light chains using polymerase chain reaction on both fixed and non-fixed material. The optimal therapy of PIOL remains to be determined: the current trends suggest that combined radiotherapy and chemotherapy, as well as intravitreal chemotherapy, are of value. Novel therapies which may have a role in the future include oral trofosfamide. *Conclusion:* Our understanding of the pathogenesis of PIOL/PCNSL remains far from complete. Intensified efforts must be made to determine the cell of origin of PIOL, as well as to establish "molecular signatures", which could be used to decrease diagnostic delay. Further studies, possibly prospective ones, are required to establish the optimal therapy for initial and recurrent disease.

Introduction

So-called primary intraocular lymphoma (PIOL) is a relatively uncommon, highly malignant non-Hodgkin lymphoma (NHL), first described as "reticulum cell sarcoma" [28], involving predominantly the retina and the vitreous [117, 145]. It may occur independently, prior or subsequent to a primary central nervous system lymphoma (PCNSL). PIOL frequently presents as a chronic, relapsing and steroid-resistant uveitis and vitritis. Because of its slow onset and ability to simulate other conditions (in terms of a "masquerade syndrome"), delays in the diagnosis of PIOL are common [4, 5, 12, 14, 19, 63, 115, 145].

Most PIOL are of B-cell origin (B-PIOL) [19, 39, 85, 109] and can be classified as diffuse large cell B-cell lymphomas (DLBCL), according to the updated World Health Organisation (WHO) lymphoma classification [81]. Intraocular lymphoma of T-cell type is less common than B-PIOL, and most cases represent an extension of mycosis fungoides (primary cutaneous T-cell lymphoma) or secondary manifestations of a systemic T-cell lym-

phoma in conjunction with systemic leukaemia (ATL/L) and is associated with human T-cell lymphotropic virus type-1 (HTLV1) infection or with acquired immunodeficiency syndrome [12, 18, 25, 33, 39, 52, 61, 66, 71, 72, 79, 84, 87, 88, 92, 94, 96, 99, 101, 119, 120, 126, 134, 135, 147–151]. Only a few cases of PIOL of T-cell origin without cutaneous or systemic involvement have been reported [31, 79, 99, 146].

Epidemiology

The exact incidence of PIOL is not known; however, it is estimated to represent 4–6% of all intracranial tumours and approximately 1–2% of all extranodal NHL [63]. Although PIOL has been described in children and adolescents [144, 153], it typically affects elderly patients, with the reported mean age in the fifth to sixth decades [12, 14, 32, 63, 115, 145]. Women are more commonly affected than men (up to 2:1), and there appears to be no differences between races [14, 32, 63, 115, 145]. PIOL may be either unilateral or bilateral on initial presentation, but approximately 80–90% of patients will ultimately develop bilateral disease [19, 20, 63, 70, 115, 145]. Intracranial lymphoma develops in 60–85% of patients with initial ocular disease, usually within 29 months [2, 19, 30, 32, 63, 145]. Recent estimates suggest that 15–25% of patients with PCNSL, which is multifocal in most cases, will have ocular disease [41, 78, 115, 143]. A yet to be explained increase in the incidence of PCNSL over the past 15 years has been reported in both immunocompetent and immunosuppressed patients, with a clear male predominance [29]. This increase, which has been reported to be up to threefold, can only partially be accounted for by the human immunodeficiency virus [50].

Symptoms and signs

When occurring prior to CNS disease, PIOL frequently masquerades as a bilateral idiopathic steroid-resistant chronic uveitis with a prominent accompanying vitritis in an elderly patient [2, 12, 13, 32, 63, 69, 70, 115, 118, 122]. Patients often complain of blurred vision, a painless loss of vision and/or "floaters". Other common presentations include photophobia or red eyes. Less common presentations include exsudative retinal detachment, fundus mass, ocular pain, glaucoma, neovascularisation, optic nerve neuropathy and a variety of chorioretinal abnormalities [63].

Involvement of the CNS by tumour cells results in both general and focal signs and symptoms [41, 77]. The most frequent single symptom reported at the time of admission is "behavioural change" [41, 56, 77]. The most common focal neurologic signs include hemiparesis in 40–50% and cerebellar signs (including ataxia) in 15–40% of cases [41, 56, 77]. Seeding of lymphoma cells into the cerebral spinal fluid has been reported in 42% of patients [56]. Although spread of PIOL/PCNSL to other regions is infrequent, it has been reported [76]; in such cases, a second peripheral malignant lymphoma should be excluded.

Ophthalmic findings in PIOL

Anterior segment

Anterior segment findings are often not observed in patients with PIOL [14]. Common findings are corneal precipitates and mild anterior flare. The cells simulate iridocyclitis and can even form a pseudohypopyon [19, 20, 63, 115, 145]. Secondary anterior segment changes include neovascularisation of the iris and iridocorneal angle with possible glaucoma. In rare circumstances, PIOL can secondarily infiltrate the anterior segment of the eye in the form of a mass in the iris or angle [142].

Posterior segment

Vitreous cells and haze ("vitritis") are typical findings and are present in most cases [19, 20, 63, 115, 145]. The characteristic fundus lesion is a flat creamy orange–yellow mass deep to the sensory retina. Lesions may be single or multiple, confluent or discrete, and may appear as multiple punctate lesions [19, 20, 63, 68, 83, 115, 145]. The presence of multiple subretinal pigment epithelial masses is considered by some to be pathognomonic of PIOL (Fig. 1) [40, 68]. They are, however, absent in a large proportion of cases with PIOL. Retinal haemorrhage is rarely prominent. Occasionally, PIOL presents as a single solitary intraocular mass [62, 97].

Diagnostic techniques

The diagnosis of PIOL can be suspected clinically when typical retinal or subretinal infiltrates are present. Additional examinations, such as ultrasonography, fluorescein angiography and high-resolution neuroimaging of the CNS, are valuable in supporting the diagnosis [118].

Imaging

Evaluation of patients with intraocular lymphoma includes ultrasonography, fluorescein angiography and high-resolution neuroimaging of the CNS with contrast. Ultrasonography allows for the evaluation of the posterior segment of eyes with opaque media, and although the findings are not specific they aid in narrowing the differential diagnosis [139]. Similarly, fluorescein angiog-

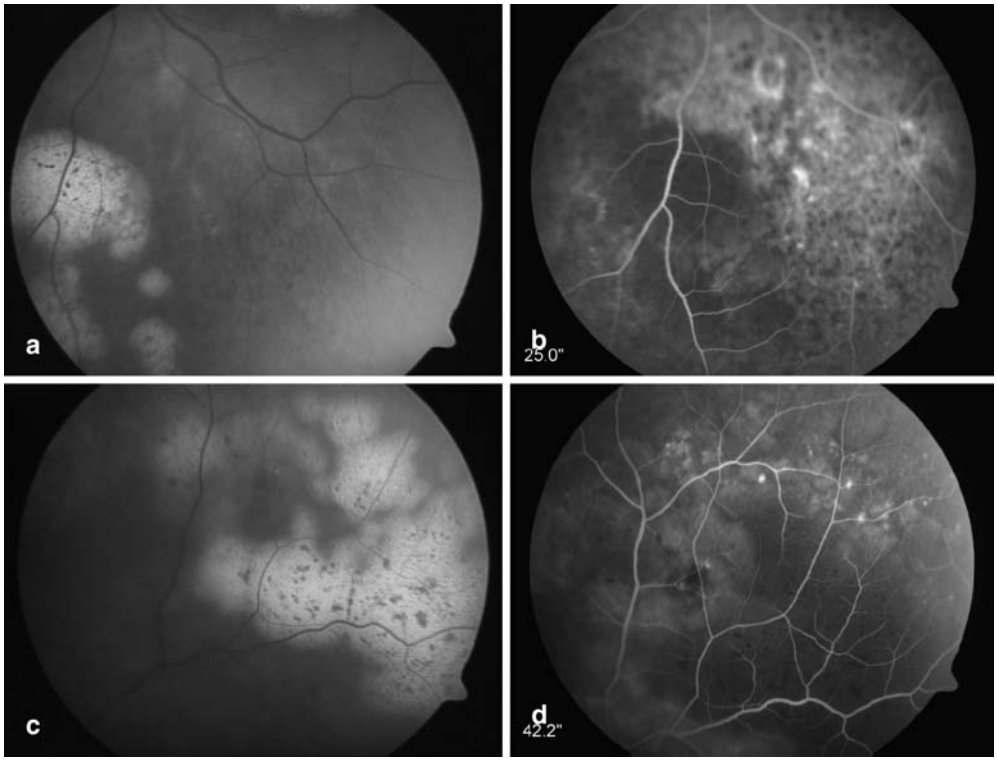

Fig. 1 **a** Multiple, confluent yellowish infiltrates under the retinal pigment epithelium in a 57-year-old patient with PIOL leading to multifocal and lobular RPE detachments. The infiltrates consist of atypical lymphoid cells and necrotic cell debris. Secondary pigmentary changes can be seen on the surface of the RPE detachments. Temporal to the RPE detachments, additional pigmentary changes at the level of the RPE and focal atrophies of the RPE can be noted. **b** Fluorescein angiography of the patient shown in (**a**). In the arteriovenous phase, the sub-RPE infiltrates cause a hypofluorescence due to the blocking of the choroidal fluorescence. No leakage or hyperfluorescence is seen within the RPE detachments, because they consist of solid celluar infiltrates and do not represent serous RPE detachments. In the area temporal to the RPE detachments, a mixed picture of hyper- and hypofluorescent areas can be seen, corresponding to hyperpigmentations and window defects in atrophic areas of the RPE as well as to areas without obvious pigmentary changes. These are thought to be a result of cellular infiltrations at the level of the RPE. Irregularities at the RPE level are the most common finding in fluorescein angiography of PIOL and are better visualised with this technique. This mixed angiographic picture of hyper and hypofluorescent areas has been compared to "leopard spots" and is thought to be typical for PIOL (but can be also be seen in other chorioretinal diseases!). **c** A 68-year-old female patient with PIOL; again, typical multifocal confluent, creamy-coloured sub-RPE infiltrations can be seen. This clinical picture is regarded as pathognomonic for PIOL by some authors [40, 68]. As in (**a**), pigmentary changes of the RPE on the surface of the RPE detachments can be seen. **d** Late arteriovenous phase of the fluorescein angiography of the patient shown in **c**. The RPE detachments resemble hypofluorescent areas in the later frames of the angiography; however, in the nasal areas of RPE detachments, a slight hyperfluorescence can be detected which is thought to be secondary to an abundance of dead cells that allow the entry of fluorescein into the areas of detached RPE. In the region bordering the RPE detachments, hyperfluorescent spots can be seen in areas of damaged RPE cells

raphy provides information in localising the layer of infiltrative involvement and the possibility of RPE disturbance in suspected PIOL patients. Depending on the extent of disease, fluorescein findings may include hypofluorescent areas due to the blocking effect of sub-RPE tumour masses, or hyperfluorescent window defects due to atrophy of the RPE (Fig. 1) [40, 68, 95, 115, 141]. Cassoux and co-workers reviewed the fluorescein angiographic findings in 44 patients with PIOL/PCNSL and reported punctate hyperfluorescent window defects in 54.5% of patients and round hypofluorescent lesions in 34% [14]. Angiographic findings typical of inflammation, such as perivascular staining or leakage, cystoid macular oedema or optic nerve head staining or leakage, are unusual in PIOL patients [141]. These findings are observed significantly more often in patients with chronic uveitis or vitritis of non-malignant pathogenesis.

Neuroimaging studies include CT, MRI, positron emission tomography (PET) and, in some centres, single photon emission CT (SPECT). Current consensus is that MRI is superior to CT in detecting lymphoid lesions in the CNS; however, both are limited in evaluation of ophthalmic disease [93]. CT usually demonstrates isodense or hyperdense lesions. On MRI, lesions show a diffuse and homogeneous pattern of enhancement with contrast in immunocompetent patients [6, 22, 43]. In AIDS patients, these lesions may demonstrate "ring" enhancement with contrast and must be distinguished from

those caused by *Toxoplasma* [22]. In most cases, the lymphoma-associated lesions are single; however, multiple focal brain lesions are observed in advanced disease. The typical sites of tumour include the basal ganglia, corpus callosum, and the periventricular subependymal areas.

Laboratory studies

Lumbar puncture to obtain cerebrospinal fluid (CSF) for cytology is indicated if the patient is thought to have PCNSL. A positive CSF has been reported in 25–33% of patients with PCNSL [42, 64, 105], and multiple lumbar punctures may be needed to establish the diagnosis of lymphoma. In a series of 12 PIOL patients, positive CSF cytology was reported in four cases [145]. Stereotactic biopsies are often required to confirm the clinical suspicion of PCNSL. In addition, serologic studies are required to exclude the other causes of uveitis mentioned below.

Cytological and histological diagnosis in ocular tissues

Vitreous biopsy

Cytological studies of vitreous biopsies remain the first step in the histomorphological diagnosis of PIOL. Such specimens are obtained by fine needle aspiration [55, 91, 112], vitreal aspiration [100] or via pars plana vitrectomy [108, 111].

Vitreous specimens demand experience both in their preparation aand in their cytomorphological interpretation, for a number of reasons. Firstly, the cellular content of vitreous samples may be sparse or of poor morphological quality, so that the diagnosis is often based on a small number of cells. Secondly, the number of reactive cells present in the specimen may greatly outnumber the neoplastic cell population. Thirdly, the tumour cells themselves are fragile (possibly due to prior steroid therapy [115]), resulting in a necrotic "dirty" background, which can make the interpretation of immunocytological stains difficult. Finally, subretinal tumours are not accessible by vitrectomy techniques unless a retinotomy is performed using a vitreous approach. False-negative diagnoses are, consequently, not uncommon [19, 32, 63, 118, 122, 145], and multiple specimens may be required before an unequivocal diagnosis of PIOL can be made [32, 118, 122, 145]. Due to the varying modes of presentation of PIOL and to the above-mentioned difficulties, diagnosis is often delayed by 8–21 months [14, 32, 63, 79, 122, 145].

The preparation of vitreous specimens for cytological evaluation varies [19, 32, 38, 51, 98, 108, 128, 145]. We are most familiar with the cytospin preparation technique using unfixed specimens which have been rapidly transported to the cytological laboratory [32]. The cytospin specimens are obtained by spinning the vitreous specimen at 500 rpm for 5 min and concentrating the cells onto glass slides. These are either air dried or fixed in Clark's fixative (12% glacial acetic acid in 70% alcohol) [147], and subsequently stained using conventional stains (e.g. May-Gruenwald-Giemsa, haematoxylin-eosin) and immunocytologically. Recently, cytofixatives (HOPE fixation; Hepes–glutamic acid buffer-mediated organic solvent protectant effect) [138], have not only proved useful in maintaining (or improving) the quality of cellular morphology of various bodily fluids, but also have allowed for further examinations such as immunocytology and molecular biological studies. We have found this to be the case with vitreous specimens subjected to HOPE fixation, whereby monoclonality of the infiltrating neoplastic B-cells could be demonstrated both in the immunocytology and in subsequent polymerase chain reaction for rearrangements of the immunoglobulin heavy chain genes (IgH-PCR) (Coupland et al., unpublished results). Such fixatives could be of use in vitreous specimens, particularly when sent from "remote" referral centres.

Cytologic diagnosis

Vitreous aspirates in PIOL consist of mature inflammatory cells, large neoplastic lymphocytes and necrotic debris (Fig. 2) [112]. The neoplastic cells are pleomorphic with minimal cytoplasm, hyperchromatic nuclei with irregular contours and prominent, sometimes multiple, nucleoli. In very occasional specimens, atypical mitotic figures could be observed. Because of the fragility of neoplastic lymphocytes, a specimen may contain numerous lytic cells. Often a large proportion of reactive inflammatory cells—consisting of small lymphocytes, macrophages and occasional neutrophilic granulocytes—are mixed within the neoplastic cell population. This, together with the cellular paucity of the specimens in general, complicates the process of trying to differentiate lymphomas from reactive processes by immunocytology [98].

Immunocytology

The vast majority of PIOL are B-cell lymphomas and therefore express B-cell antigens, such as CD20, CD79a or PAX5 (also known as BSAP) [(Fig. 2)]. In the rare cases of primary intraocular T-cell lymphoma, the neoplastic cells demonstrate positivity for T-cell markers such as CD3 and CD8, possibly with loss of T-cell receptor β chain expression [31, 72, 99].

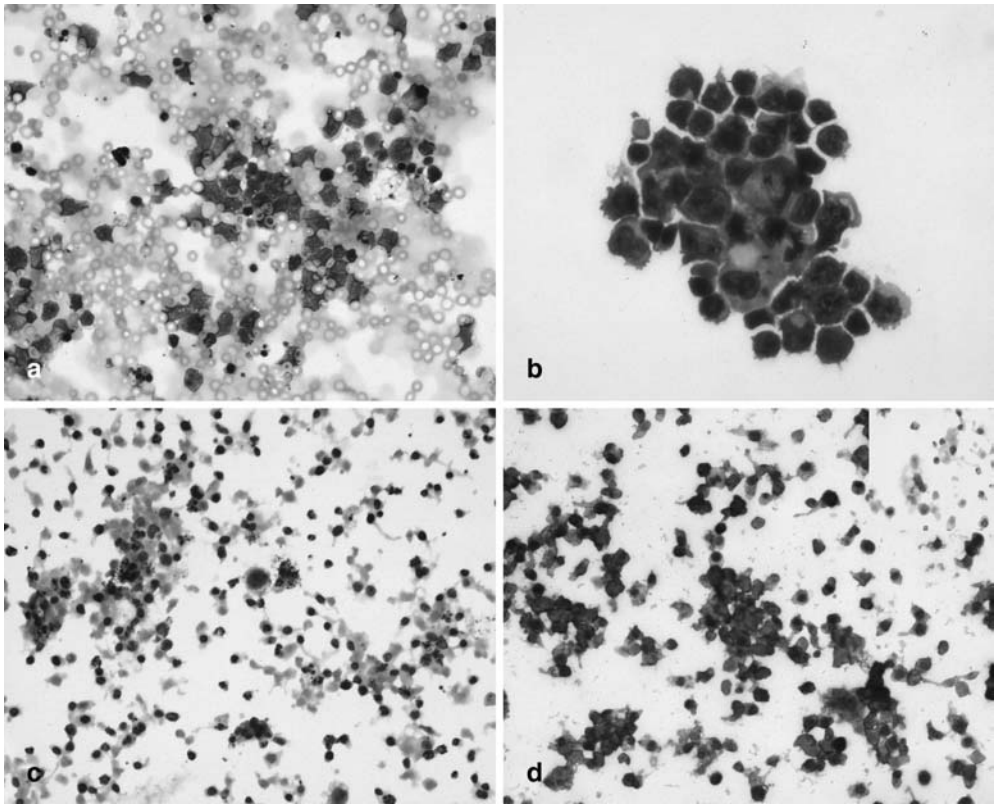

Fig. 2 **a** Cellular dense vitreous aspirate containing erythrocytes and pleomorphic lymphocytic blasts with **b** large irregular nuclei and prominent nucleoli (MGG, original magnification ×200 and ×400 respectively). **c** A further vitreous aspirate consisting of a large number of lytic cells (MGG, original magnification ×200) and **d** atypical B-lymphocytes (APAAP, original magnification ×200)

Chorioretinal biopsy and enucleation

If vitreous samples fail to demonstrate lymphoma cells, retinal and chorioretinal biopsies or subretinal aspiration can be performed [10, 24, 32, 90, 95, 103, 113, 118]. These chorioretinal biopsies can be fixed in 4%-buffered formalin, allowing for easier specimen handling. A larger range of immunohistochemical investigations can be performed on these specimens than on vitreous aspirates. This, in turn, increases the chance of diagnosing or excluding a PIOL. Further, an exact subtyping of the malignant lymphoma when present can usually be undertaken, enabling differentiation between a primary and a secondary ocular manifestation of systemic lymphoma. In rare cases, when the eye becomes blind and painful due to secondary glaucoma and/or complete retinal detachment, enucleation is unavoidable and can lead to a definitive diagnosis.

Conventional histology of B-PIOL in the chorioretinal biopsy demonstrates an infiltrate of atypical lymphocytes in the retina (Fig. 3). The neoplastic cells are medium to large in size with basophilic cytoplasm, oval-shaped nuclei and conspicuous nucleoli. A large number of mitotic figures can be observed. In the enucleated eye, clusters of cells may be seen in the neurosensory retina (often perivascularly) (Fig. 3), in the subretinal space, and between the retinal pigment epithelium and Bruch's membrane. Reactive lymphocytic infiltrates may be present in the adjacent choroid. The tumour cells are positive for the above-mentioned B-cell antigens, usually demonstrate a monotypical expression of an immunoglobulin molecule light and/or heavy chain, and demonstrate a large growth fraction (average 80%) using the MIB1 antibody, directed against the Ki-67 antigen. In addition, B-PIOL cells express the proteins BCL-2, BCL-6 and multiple myeloma protein 1 (MUM1; also known as IRF4) (Fig. 3) [32] The expression of these proteins by the tumour cells is in accordance with findings in DLBCL in other locations [3, 81]. In normal tissue, the expression of BCL-6 and MUM1/IRF4 is mutually exclusive [54]. Approximately 50% of MUM1/IRF4 + DLBCL also express BCL-6, suggesting that expression of these proteins is deregulated in these lymphomas [54]. Together with the above-described expression of BCL-2 protein, positivity of the PIOL tumour cells for BCL-6 protein would suggest a germinal centre cell being the neoplastic cell of origin in this lymphoma. This notion would be supported to some extent by recent evidence demonstrating the presence of somatic mutations in the variable region of the immunoglobulin gene ([36]; F. Davi, personal communication). Further investigations on a larger number of tissue specimens, however, are required to underline this hypothesis and to determine whether these proteins are of prognostic significance.

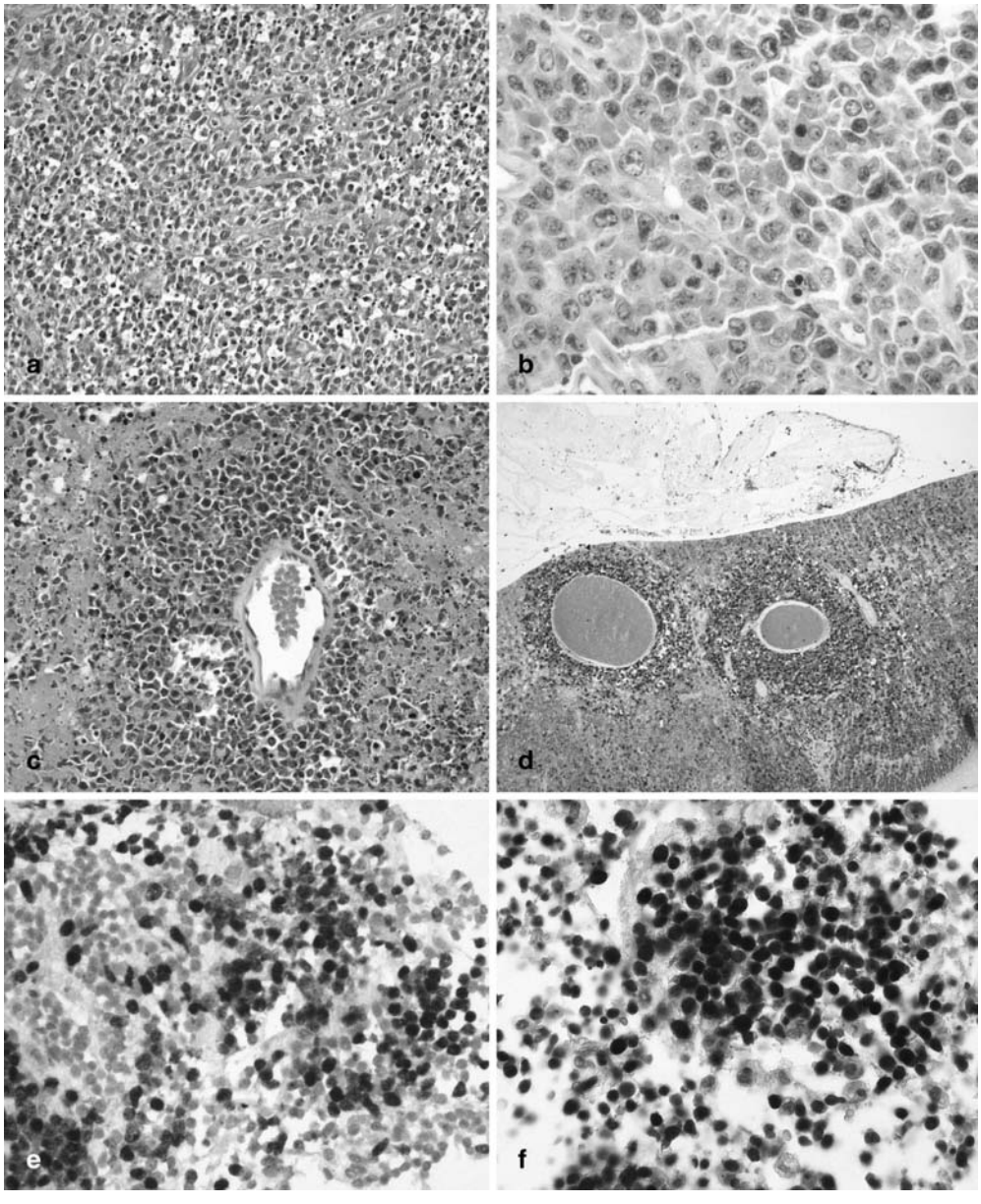

Fig. 3 **a** A chorioretinal biopsy containing a dense infiltrate of atypical lymphocytic cells (PAS stain, original magnification ×200). **b** The neoplastic cells are medium to large in size with a moderate amount of cytoplasm and pleomorphic nuclei (Giemsa, original magnification ×400). **c** An enucleation specimen demonstrating the typical perivascular arrangement of the tumour cells (HE, original magnification ×200). Immunoreactivity of the neoplastic lymphocytes **d** for the B-cell antigen CD20, **e** for MUM1/IRF4 and **f** for BCL-6 (APAAP, original magnification ×400)

Biochemical and molecular analysis of PIOL

In order to derive more diagnostic data from vitreous specimens, various additional investigations have been performed as adjuncts to the frontline morphological and immunocytological studies. These include flow cytometry [39], determination of cytokine concentrations, particularly interleukin 10 (IL-10) [14, 16, 146], PCR seeking monoclonal rearrangements of immmunoglobulin heavy (IgH) or light (IgL) chains in B-cell lymphoma or T-cell receptor genes in T-cell lymphoma [32, 86, 129, 147], and determination of CDR3 (complementary determining region) polymorphisms in the variable region of the immunoglobulin gene [73].

Flow cytometry and cytokine analysis

Flow cytometry allows for the immunophenotyping of cells in vitreous specimens and for the demonstration of monoclonality. The accuracy of flow cytometry compared with cytology varies among centres [18, 39, 122]. Cytokine concentration analysis in the vitreous and the anterior chamber appears also to be of use in aiding the differentiation between inflammatory and neoplastic uveitis. Whereas IL-6 is produced by inflammatory cells, IL-10 is produced by malignant B-lymphocytes [16]. IL-10 concentrations above 100 pg/ml in the vitreous and of 70 pg/ml or more in the anterior chamber are suggestive of B-PIOL [107]. Furthermore, IL-10 levels are used in some

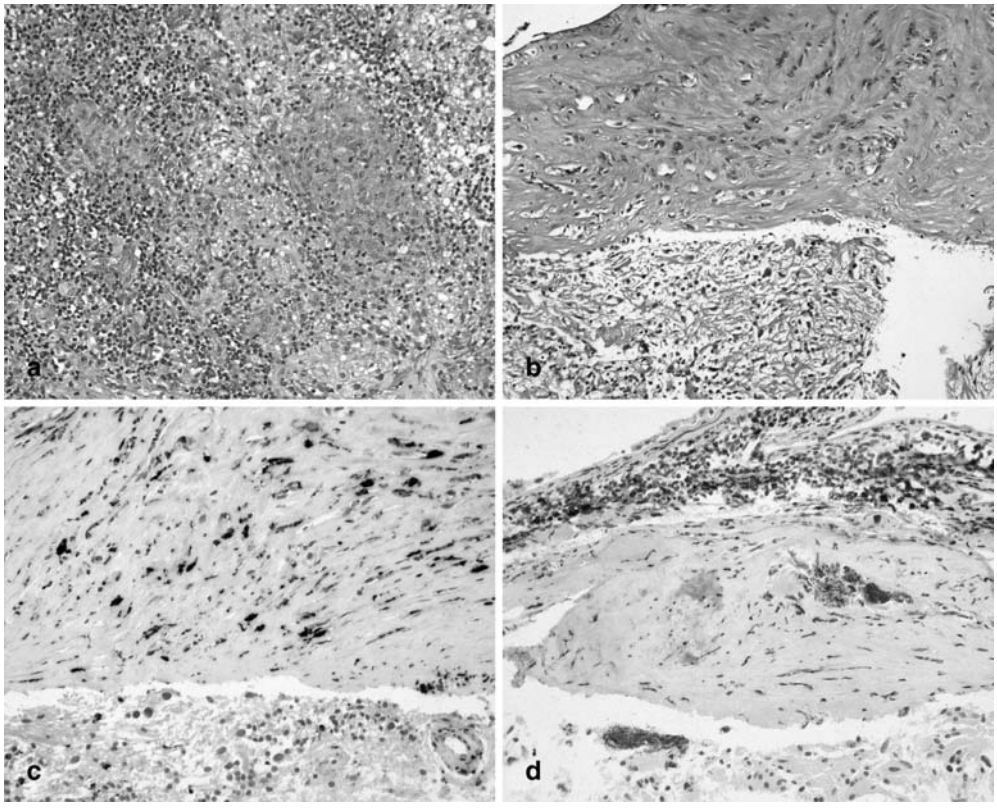

Fig. 4 **a** Chorioretinal biopsy demonstrating a granulomatous inflammatory infiltrate with "sarcoid-like" granulomas in a patient with sarcoidosis (HE, original magnification ×200). **b–d** Chorioretinal biopsy in a patient with gliotic and sclerotic changes of the retina forming **b** a disciform plaque (HE, original magnification ×100) with **c** admixed macrophages (APAAP, CD68 clone PGM1, original magnification ×400) and **d** a minimal reactive lymphocytic infiltrate in the adjacent choroids (APAAP, CD3, original magnification ×200)

centres for treatment monitoring [107]. It remains uncertain, however, whether an increase in IL-10 levels occurs in the vitreous of patients with T-PIOL. Laboratories relying exclusively on vitreous IL-10 levels for the diagnosis of B-PIOL could, therefore, miss the small proportion of PIOL that are T-cell related.

Assessment of clonality using IgH-PCR and TCR-PCR

IgH-PCR and TCR-PCR are very useful adjunct examinations, as demonstration of gene rearrangements, which do not occur at any significant frequency in normal B-cell or T-cell differentiation, is strong evidence for the diagnosis of PIOL. These examinations can be performed on unfixed vitreous specimens as well as on fixed and paraffin-embedded tissue biopsies [32]. The results of the IgH-PCR should always be interpreted in conjunction with the cytomorphology and with caution, particularly in paucicellular vitreous biopsies where "pseudoclones" could be amplified. In enucleated eyes, where the tumour cell population may be small compared with the reactive cell population, specific removal of the tumour cells, either by cutting into the paraffin block ("macrodissection") or from the cut section ("microdissection") [129], may increase the possibility of obtaining an amplification product. Due to numerous somatic mutations in the variable region of the immunoglobulin gene, it may not be possible to obtain a monoclonal amplification product in the IgH-PCR. Newer primers however have increased the chances of primer binding and, therefore, of detecting monoclonal populations [47]. Recently, we were able to demonstrate using IgH-PCR and GeneScan analysis that the clonal population of B-cells in the vitreous and in the cerebral tissue in a patient with PIOL/PCNSL was derived from the same precursor cell [36]. This is one of the first pieces of molecular biological evidence supporting the widely held assumption that the lymphomatous manifestations in the brain and the eye represent the one and the same tumour.

Clinical differential diagnosis

The differential diagnosis of PIOL includes other intraocular manifestations of lymphoma (Table 1), metastatic tumour; amelanotic melanoma; as well as non-neoplastic diseases of the uvea (Table 2) [(Fig. 4)]. The other lymphomatous manifestations which can occur in the eye include (a) the primary lymphomas arising primarily in the uveal tract and (b) secondary intraocular (mainly choroidal) involvement of systemic lymphoma, usually leukaemia (Table 1) [11, 23, 26, 34, 35, 74, 89, 117, 121, 127]. Due to space limitations, only the former will be discussed here.

Table 1 Intraocular lymphoma manifestations and relationship to anatomical site

	Anatomical location	Lymphoma subtype[a]	Immunophenotype
Primary intraocular lymphoma	Usually retina perivascular or in subretinal space	Usually diffuse large cell B-cell lymphoma (DLBCL) [(T-cell lymphomas rare)]	CD79a+, CD20+, PAX5+, CD10+/–, BCL2+/–, BCL6 + mostly, MUM1+/–, MIB1 often >60%
Primary uveal lymphoma	Choroid (iris rare)	Extranodal marginal zone B-cell lymphoma (EMZL)	CD79a+, CD20+, PAX5+, CD43+ mostly, BCL2+, CD10–, BCL6–, IgM+, MIB1 often 5–15%
Secondary intraocular lymphoma	Usually choroid	Dependent on systemic NHL	Dependent on systemic NHL

[a] According to the new WHO lymphoma classification [81]

Table 2 Diseases of the chorioretina considered in the differential diagnosis of PIOL

Toxoplasmosis
Frosted branch angiitis
Herpes zoster ophthalmicus
Cytomegalovirus retinitis
Syphilis
Tuberculosis
Sarcoidosis (Fig. 4)
Acute posterior multifocal placoid pigment epitheliopathy
Acute retinal necrosis
Retinal vasculitis
Branch retinal artery obstruction with coexistent multifocal chorioretinal scars
Birdshot choroidopathy

The primary uveal lymphomas are probably the most infrequent intraocular lymphomas: they can be divided into those exceptionally rare cases arising in the iris [151, 152], and those in the choroid. With regard to the primary choroidal lymphomas, 65 cases have been described since 1920 [9, 11, 17, 21, 23, 26, 27, 35, 37, 46–49, 53, 67, 74, 80, 83, 105, 124, 125, 130, 131, 137, 155]. The primary choroidal lymphomas differ in a number of respects to PIOL. Firstly, the primary choroidal lymphomas are clinically indolent, and have been attributed a number of terms in the past, including "uveal pseudotumours". They usually occur unilaterally in men in the fifth decade. Typical presenting symptoms include a recurrent episodes of blurred vision, painless loss of vision and metamorphopsia due to secondary serous detachment of the macula. There may be an initial response to steroid therapy. Ultimately, a diffuse thickening of the uveal tract becomes obvious on fundoscopy, and, in some patients, subconjunctival or episcleral extension may occur. The lymphomas are commonly low-grade malignant B-cell, and have been recently sub-typed as "extranodal marginal zone B-cell lymphomas" (EMZL) of MALT type, according to the REAL classification [35]. In distinct contrast to the high-grade malignant PIOL arising primarily in the retina, the overall survival of patients with primary choroidal EMZL is very good, with the development of systemic disease occurring in a minority of patients following treatment [35]. Involvement of the CNS by primary uveal lymphoma is exceptional.

Therefore, choroidal EMZL and retinal DLBCL are lymphomas both occurring primarily in the eye but with differing clinical pictures, courses and prognoses. On the basis of this, one questions the suitability of the rather vague but established term "primary intraocular lymphoma" for only those lymphomas arising in the retina and the vitreous. The terms "primary vitreoretinal lymphoma"and "primary uveal lymphoma" with sub-typing according to modern lymphoma classifications may possibly be more appropriate and accurate.

Treatment

The treatment recommendations for PIOL with or without CNS disease are in flux and are still controversial. Due to the sensitivity of lymphoma cells to radiation, radiotherapy alone to the eyes and CNS was the main form of treatment for PIOL with or without PCNSL in the past. Although it gave high rates of initial response, most patients usually succumbed to recurrent disease, and died with a median survival of 12–20 months [57, 59, 102, 110]. In those patients who survived for longer periods, ocular radiation was associated with delayed toxicity, including radiation retinopathy, optic neuropathy, dry eye, corneal epithelial defects, loss of limbal stem cells, cataracts and glaucoma [13]. Furthermore, radiation-associated cognitive defects after whole brain irradiation were observed in up to 40% of PIOL/PCNSL patients over 50 years in age [65].

Significant advances in the treatment of PIOL/PCNSL were achieved with the introduction of combined chemoradiation to the CNS and reduced ocular radiation [20]. With multimodality therapy, including boosted radiation dose (5–10 Gy) to the spinal cord and intrathecal methotrexate (MTX), vision could be improved and the median survival prolonged. Persisting problems in treatment included the relatively high rate of recurrences in ocular disease (up to 50% of patients), as well as delayed neurotoxicity [1, 44]. Once tumour relapse occurs, addi-

tional treatment with systemic chemotherapy is often required, leading to augmentation of cumulative treatment toxicity [116].

Consequently most centres propose systemic chemotherapy only for combined PIOL/PCNSL [43, 140]. Systemic chemotherapy offers the possibility of simultaneous treatment of intracranial and intraocular disease, with a possible reduction in the risk of intraocular and neurotoxicity compared with radiotherapy. High-dose MTX is included in most regimens, administered systemically due to its penetration of the blood–brain barrier and blood–retinal barrier [7]. Other systemic trials have used cytosine arabinoside (Ara-C) with or without MTX [8, 116, 136, 140]. However, the efficacy of systemic chemotherapy as an exclusive treatment for PIOL is dependent on intraocular pharmacokinetics. For example, seven of nine patients with PIOL treated with high-dose MTX alone (8 g/m^2 body surface area) responded in the eye, with persisting remission in four patients after 8–36+ months [7]. Micromolar MTX concentrations were present in both ocular chambers 4 h after the infusion in eight of eight patients. Following systemic application of high-dose Ara-C, therapeutic levels in intraocular fluids together with a response of 15 months and longer have been documented [8]. However, several studies [134, 136] reported a discrepant response of lymphoma manifestation in the brain and in the eye, suggesting that penetration of cytostatics into these compartments may differ and that the maintenance of sufficient levels of MTX in the vitreous is difficult.

Both systemically administered MTX and Ara-C result in ocular side effects that include periorbital oedema, conjunctivitis and conjunctival hyperaemia, keratitis and photophobia [140]. Proposals made to reduce the effects of systemic chemotherapy include the administration of intrathecal MTX and/or Ara-C [132, 104].

Promising results for PIOL were obtained with high-dose chemotherapy followed by autologous bone marrow [133]. Nine of 12 patients with refractory or relapsed PIOL treated with high-dose thiotepa, busulfan and cyclophosphamide followed by hematopoietic stem cell rescue achieved complete response in the brain and the eye. Median overall survival was 53+ months after relapse. However, the therapy was toxic, with death occurring during treatment in five of seven patients older than 60 years [133].

Intravitreal methotrexate has been used to reduce the extent of intraocular tumour in patients who have undergone chemotherapy with or without radiation with good success at preserving vision [60, 75]. With repeated intravitreal injections of cytostatics in patients with PIOL, a local tumour response may be achieved.

Possible future therapies could include oral trofosfamide [82] and an anti-CD20 antibody known as rituximab, already applied in systemic lymphoma. Intrathecal and intravitreal administration of the latter could be considered for the treatment of PIOL and PCNSL due to its poor penetration of the blood–brain and blood–ocular barriers [58, 114, 123].

Prognosis of PIOL

Although many patients with PIOL succumb to CNS disease within 2 years, the median survival of PIOL/PCNSL has increased from 1.0–1.5 to over 3 years with newer therapies [45]. The data on the subject of prognostic parameters in PIOL/PCNSL is limited to small treatment series due to the relative rarity of this disease. Some authors suggest that tumour cell positivity for BCL6 protein in PCNSL is a predictor of a poorer prognosis [56]. PIOL with the translocation $t(14;18)$ has been suggested to be more aggressive clinically [15]. Larger collaborative studies in clinically well-defined patient series are required to determine whether any particular subtypes of PIOL/PCNSL should be treated more aggressively.

Summary

Intraocular lymphoma manifestations can divided into three major groups: (a) the high-grade malignant lymphomas (usually DLBCL) occurring in the retina (presently PIOL), often associated with PCNSL; (b) the primary lymphomas arising primarily in the uveal tract (choroid), which are most commonly low-grade malignant B-cell lymphomas (EMZL); and (c) intraocular involvement of systemic lymphoma (mainly choroidal). The iris is very rarely involved in primary and secondary manifestations of lymphoma.

The histopathological diagnosis of PIOL is often extremely difficult due to the often sparse and necrotic material which is received for investigation. Since the disease demonstrates a very aggressive course, with the development of cerebral manifestation in a large number of patients, PIOL should be excluded in all elderly patients presenting with a chronic steroid-resistant uveitis. Cytological examination of rapidly transported, unfixed vitreal specimens remains the gold standard in exclusion of neoplastic disease in patients with idiopathic chronic uveitis. Direct communication between ophthalmic surgeon and pathologist is essential to optimise evaluation of vitreous specimens. Vitreous samples are usually considerably less cellular than the clinical appearance would suggest, and the diagnosis of PIOL is often based on a limited number of cells. Various techniques including IL-10 concentrations as well as IgH-PCR and TCR-γ-PCR have proved to be useful adjuncts in diagnosing PIOL. Chorioretinal biopsies increase the chances of diagnosing or excluding a PIOL. Further, they allow for exact subtyping of the malignant lymphoma when present, en-

abling exclusion of a primary uveal lymphoma, a secondary involvement of the eye by a systemic NHL, as well as of a reactive disease process. Although PIOL of T-cell type occur, most PIOL are of B-cell type (DLBCL according to the WHO lymphoma classification), with an immunophenotype suggesting an origin from germinal centre cells. Further studies of B-PIOL are required to confirm the cellular origin of these tumour cells and to determine whether there are any immunohistochemical or molecular biological predictors of prognostic and therapeutic significance.

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