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COMMENT

Learning points in intraocular lymphoma

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Intraocular lymphoma (IOL) has two distinct forms, primary intraocular lymphoma (PIOL) that is mainly a sub-type of primary central nervous system lymphoma (typically a diffuse large B-cell lymphoma) [1] and secondary IOL, which originates as a systemic non-Hodgkin's lymphoma (rarely Hodgkin's type as well) and spreads to the eye as a metastasis [2]. Rarely, intraocular T-cell lymphoma can be found in association with cutaneous T-cell lymphoma, NK T-cell lymphoma or adult T-cell lymphoma. IOL has a low incidence, representing an estimated 1.86% of ocular malignant tumours [3], up to 2.5% of uveitis cases [4], 1–2% of extranodal lymphomas and 4–6% of primary brain tumours [3]. It has typically been described as having no gender partiality and an age of onset around the fifth and sixth decades of life [5], although there are cases involving children and young adults [6]. Though the aetiology of IOL is uncertain [3], genetic sequencing revealed in cases the presence of Epstein–Barr virus RNA as well as *Toxoplasma Gondii* DNA [7, 8]. The rising trend in cases has been put down to the surge of immunosuppressed and immunodeficient patients, the advancement of diagnostic procedures and the rise in life expectancy [3].

Diagnosis of PIOL is challenging as it is a masquerade syndrome, clinically imitating uveitis, white dot syndromes or other neoplasms [6] and will also initially respond to corticosteroid treatment [3]. As PIOL tends to occur in older patients, suspicion should be raised in any case of new-onset uveitis over the age of 60. The most frequent early symptoms include floaters and blurred vision [9]. Visual acuity is generally better than expected looking at the clinical signs [6]. Intermediate/posterior uveitis is the most common presenting sign, with abundant vitreous cells found in clumps or veils. It is important to note there is often no anterior segment inflammation and the eye is mostly quiet and white [3]. Cystoid macular oedema (CMO) is usually absent as the malignant cells do not cause CMO in the same way that inflammatory cells in uveitis do. Overall, 64–83% of cases are bilateral and 56–90% of patients with PIOL will present with or acquire CNS lesion symptoms, the most common being focal deficits, behaviour and personality alterations as well as cognitive impairment [3].

Typical findings on ocular imaging can facilitate achieving the diagnosis (Table 1). Once there is clinical suspicion of IOL samples of ocular fluid (primarily vitreous) must be taken to confirm the diagnosis. As IOL can respond to treatment with systemic corticosteroids, temporarily eliminating or reducing cells from the vitreous, it is important to stop treatment for at least 2 weeks prior to sampling. Histological analysis remains the cornerstone of diagnosis. False negatives are not uncommon due to rapid cell degeneration within samples, too few cells within the sample or conversely a plethora of other cells and debris making it hard to find the lymphoma cells [10]. Cytokine analysis of the vitreous samples can support the diagnosis and elevated interleukin (IL)-10 levels with an IL-10:IL-6 ratio > 1.0 suggest a diagnosis of PIOL [11]. Elevated IL-6 levels are typically found in inflammatory conditions. Flow cytometry can be used to identify monoclonal B-cell populations, but the small sample size and number of cells limit the usefulness of this test. Molecular analysis of the samples can detect *IgH* gene rearrangements in B-cell lymphoma or T-cell gene rearrangements in T-cell lymphoma [12]. If the vitreous sample is negative but clinical suspicion remains high then retinal or chorioretinal biopsies should be considered [13].

Once a diagnosis is made it is imperative to get the oncology team involved for a complete systemic review, CNS evaluation including LP, brain MRI and treatment [14]. There are no official guidelines for treatment, but strategies include ocular treatments such as single or multiple

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Table 1 Clinical appearances and investigations of intraocular lymphoma.

Clinical appearance of PIOL [3]	Investigations
Intermediate/posterior uveitis Vitreous haze Vitreous cells (in sheets or clumps) Posterior vitreous detachment Vitreous haemorrhage Leopard skin pigmentation Exudative retinal detachment Granulomatous panuveitis	**Optical coherence tomography (OCT):** Hyperreflective material accumulation in the intraretinal and subretinal pigment epithelial spaces [20] **Fundus autofluorescence:** Hyperautofluorescent areas can be active subretinal pigment epithelium deposits, and hypoautofluorescent areas can be where malignant cells may have been previously [21] **B-scan ultrasound:** Clusters of moderately condensed punctate echoes or eccentric masses within the retina [22] **Fluorescein angiography (FA):** Mottling, granularity, and late staining. Classic 'leopard skin pigmentation' pattern spread over a mass [23] **Indocyanine green angiography (IGA):** (rare) round clustered hypofluorescent lesions [23] **Fine needle vitreous aspiration/pars plana vitrectomy specimen:** Positive histology, elevated IL-10 levels, gene rearrangement, flow cytometry **Retinal or chorioretinal biopsies:** Positive histology

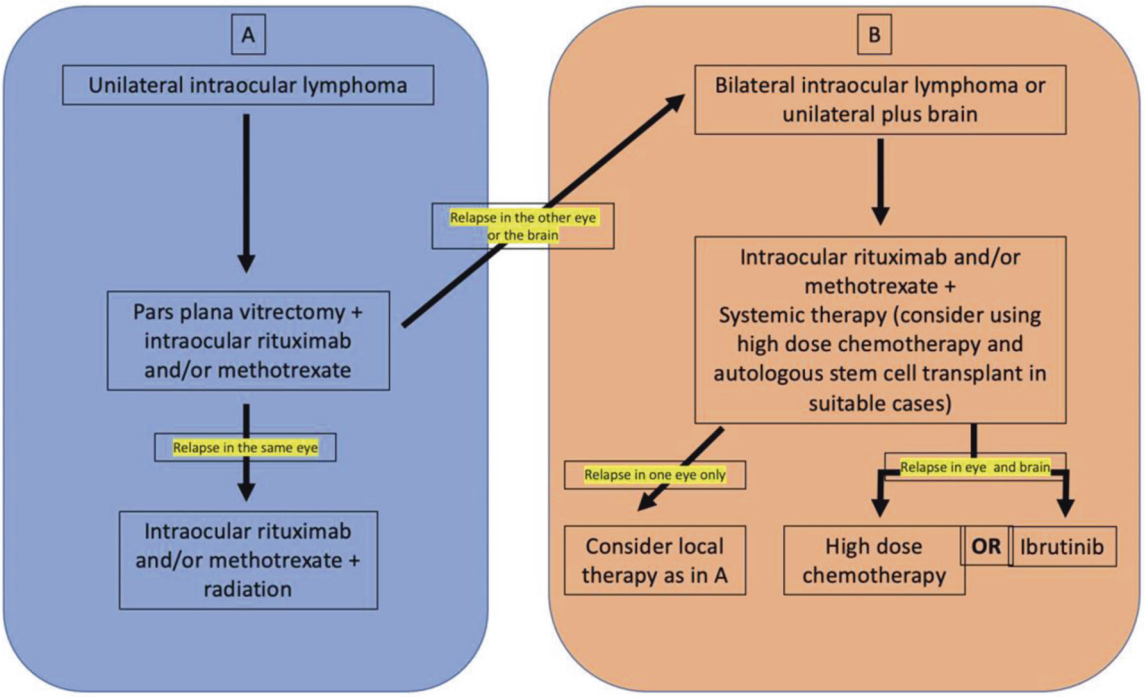

Fig. 1 Treatment algorithm for intraocular lymphoma. Panel **A** shows the treatment algorithm for unilateral intraocular lymphoma and panel **B** states the treatment algorithm for bilateral intraocular lymphoma, adjusted from [24].

intravitreal methotrexate (MTX) injections [15], intravitreal Rituximab (anti-CD20 monoclonal antibody) and/or binocular external beam radiation [6]. If the presentation is bilateral or there is CNS involvement, systemic chemotherapy with or without autologous stem cell transplantation [16] are also considered [6]. Ibrutinib is a tyrosine kinase inhibitor that shows promising results for relapse or refractory PIOL [17]. Relapses are also treated with repeat intraocular injections of MTX or rituximab (Fig. 1).

Survival times are difficult to interpret as cases are rare and there is often a delay in treatment due to misdiagnosis. Reported IOL survival time is increasing and was recently reported as 44 months [18]. We are also now seeing long-term disease-free survivors [19]. Within PIOL survival is improved if there is no CNS involvement [19].

Conclusions and learning points

- Age should not be part of the diagnostic criteria as increasing numbers of young people are being diagnosed.

- In PIOL, visual acuity is generally much better than one would expect looking at the clinical signs and CMO is usually absent.
- Imaging may be useful in aiding diagnosis.
- Although histology is the gold standard, use of multiple tests, including IL-10 levels and molecular analysis, can increase the chance of diagnosis.
- Survival has much improved for IOL, with greater therapeutic options.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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