Intraocular Lymphoma: A Review

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Abstract

Intraocular lymphoma is a rare disease but its oncologic nature makes it important to diagnose. However, the diagnosis is often delayed because of a specific clinical presentation usually as a masquerade syndrome of posterior chronic uveitis. Moreover, to confirm diagnosis, ocular sample for histological proof is mandatory but the sensitivity of this analysis remains low. This review aims to describe the main clinical characteristics and diagnosis tools for primary vitreoretinal and uveal lymphomas in order to improve early recognition of these pathologies in daily practice. We discuss treatment outlines and point out to the new perspectives of treatment and management challenges.

Keywords: Intraocular lymphoma; Vitreoretinal lymphoma; Uveal lymphoma

Introduction

Intraocular Lymphoma (IOL) is a rare pathology, but its oncologic nature and bad prognosis require a prompt diagnosis to optimize treatment and outcome. Diagnosis means and treatments are constantly evolving. The purpose of this review is to classify different types of intraocular lymphomas with their clinical characteristics, diagnostic clues and therapeutic outlines.

Classification

IOL can be classified according to their histology, anatomical localization, and their primary or secondary nature (Figure 1). Histologically, lymphoma is a malignant proliferation of lymphoid cells; it can be divided in Hodgkin's Lymphoma (HL) or Non-Hodgkin's Lymphoma (NHL). The intraocular infiltration in HL is very rare. NHL can be furthermore divided in B-cell or T-cell lymphoma. More than 90% of ocular lymphomas are mature B-cell NHL, while T-cell NHL account for less than 15% of all adult NHL and rarely involve the eye [1,2].

Anatomically, ocular lymphoma can be intraocular or adnexal. Intraocular localization includes Vitreoretinal Lymphoma (VRL) infiltrating the retina, vitreous and optic nerve; and Uveal Lymphoma (UL) infiltrating the choroid, ciliary bodies and iris. More precisely on OCT, UL involve the choroid posterior to the Bruch membrane; conversely, VRL infiltrate the vitreous and retina anterior to the Bruch membrane [3]. IOL is either primary or secondary to a systemic lymphoma that can involve any intraocular structure (uvea, retina, vitreous and optic nerve).

Primary Vitreoretinal Lymphoma (PVRL) is mostly high grade Diffuse Large B-Cell Lymphoma (DLBCL) [4]. Primary uveal lymphoma and adnexal lymphoma are low grade small B-cell lymphoma: Extranodal Marginal Zone Lymphoma (EMZL) a in 60% to 80% of cases or follicular type [1,5-7]. Secondary uveal lymphoma is most of the time a metastasis of high-grade systemic NHL of T-cell or less often B-cell or NK/T-cell type [4,8,9]. Some authors suggest that we should consider adnexal and uveal lymphoma as variants of a same entity since they show histological et clinical similarities [7,10,11].

Epidemiology

We lack a reliable multicenter database to establish epidemiological data. IOL affect elderly people (mean age is 70 years old), without sex or racial predilection [6,12]. Incidence is rising, probably related to increase in life expectancy and better diagnostic tools [5]. The most frequent IOL is PVRL and accounts only for 0.1% of intraocular tumors [11]. PVRL can be associated to Primary Central Nervous System Lymphoma (PCNSL) at diagnosis in 15% to 25% of cases, in which case it should be labeled as Primary Oculocerebral Lymphoma (POCL). If it is isolated at diagnosis, there is a risk of extension to the Central Nervous System (CNS) of 56% to 90% of cases during the follow-up [12]. The most common primary UL and secondary IOL is choroidal lymphoma [2,11,12].

Primary Vitreoretinal Lymphomas

Pathophysiology

Pathophysiology of PVRL remains unclear. Here we list some theories which could help explain the process and discover new therapeutic targets.
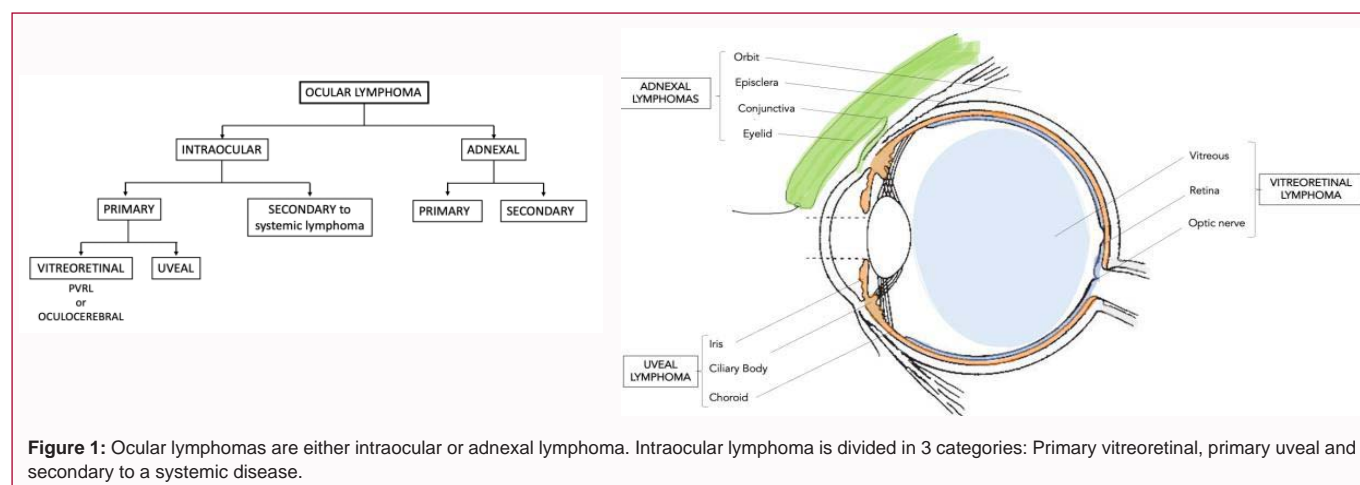
- The eye and CNS are both immune-privileged environment and similarities exist between blood-ocular barrier and blood-brain barrier.

- The tumoral transformation is believed to happen outside the eye or brain; then the tumoral cells are attracted to the immune-privileged environment thanks to specific chemokines. SDF-1 (Stromal cell Derived Factor 1) and BCL (B-Cell Ligand) have been detected in the RPE layer and bind to tumoral cell receptors CXCR-4 and CXCR-5. They could become therapeutic target [6,13-15].

- Malignant lymphoid cells of PVRL show specific immune profile suggesting an emergence from an advanced state of differentiation in germinal centers. They express many hypersomatic mutations of immunoglobulin genes, suggesting a role of antigen selection as a trigger to neoplastic transformation. The causal antigen(s) are not yet identified, except in immunocompromised patients for whom the role of proto-oncogene Epstein-Barr virus is proven [6,16]. Immunoglobulin gene mutations MYD88 and CD79B are frequently found in lymphomas of immune-privileged sites and these pathways are new therapeutic targets [6,15,17].

- Animal experimental data showed that the T-cell antitumoral response is based upon CD3+ T-Cell with Th1 immune profile. These T-cells are inhibited *in vivo*; hence their stimulation *in situ* to strengthen antitumoral immunity is also a therapeutic target.

Clinical features

PVRL can be diagnosed on routine ocular screening in patients with central nervous system lymphoma, or manifest as a masquerade syndrome of uveitis, which is defined by any neoplastic or non-neoplastic pathology that mimics uveitis and leads to diagnosis delay. PVRL can mimic any type of uveitis, most often a chronic intermediate or posterior uveitis with partial response to corticosteroid therapy [13,14]. The lack of specificity of clinical presentation results in a diagnosis delay of 6 to 40 months on average [18,19]. Symptoms are insidious, most often patients complain of blurred vision and floaters; however, visual acuity is often moderately altered in proportion to the vitritis [14. It is bilateral in 2/3 of cases, but often asymmetric at presentation [5,12,18]. The most frequent clinical sign is vitritis (60% of cases) [11,16], with typical clumps of lymphoma cells along the peripheral vitreous fibrils. The second most frequent clinical sign is intra- or sub-retinal infiltrates, cream-colored and multifocal (50% of cases) [14,18]. They tend to coalesce and as they grow in size and get remote from the vascular supply, they become necrotic and leave pigmentary epithelial alterations [11,17]. The retinal infiltrates can mimic white dot syndrome, retinitis foci or chorioretinitis scar [11,13,20]. Choroidal infiltration usually does not occur [17]. Rare manifestations reported are exudative retinal detachment (Figure 2), granulomatous panuveitis, vasculitis, retinal hemorrhages, optic nerve infiltration [5,11,12,21]. Fundus can be normal in 30% of cases [14]. Macular edema is common in uveitis but rare in PVRL. A case series at the Mayo Clinic showed that many confounding factors could explain most of macular edema in PVRL patients (radiation retinopathy, intraocular surgery, systemic chemotherapy, epiretinal membrane prior to diagnosis). They find a 10% incidence of macular edema [22]. Cassoux et al. in Paris report the lowest incidence of 2.46% [23]. Anterior chamber reaction is rare and if present very mild; cellular keratic precipitates can sometimes mimic Fuch's uveitis [12,14,18]. Rare manifestations reported are posterior capsular opacification, iris heterochromia, secondary glaucoma [13,14].

On fluorescein angiography, retinal infiltrates appear hypofluorescent by masking effect at early and late phases; RPE alterations appear hyperfluorescent by window defects [18]. This alternation of hypo and hyperfluorescent spots lead to the well-described aspect of leopard retinopathy; however, it is not pathognomonic [5]. Infiltrates are rarely observed on indocyanine green angiography [14]. In fundus autofluorescence they appear as hyperautofluorescent spots surrounded by hypoautofluorescent outer retinal atrophy [14] (Figure 3). On OCT, hyperreflective deposits are found between the RPE and Bruch membrane [18]. Barry et al. described different OCT characteristics found in PVRL: Hyperreflective nodular sub-retinal foci (21.9%), hyperreflective sub-retinal band (31.3%), hyperreflective intraretinal foci (18.9%), hyperreflective foci in the posterior vitreous (15.6%) and sub-RPE deposits (9.4%). Lymphoma cells infiltrates typically respect anatomical planes on OCT [24]. A 2019 case series suggested the existence of precursor lesions as hyperreflective columns affecting the entire length of the neuroretina, near retinal vessels [25]. The association of OCT, fluo-angiography and indocyanine angiography has a positive predictive value of 89% and negative predictive value of 85% [16].
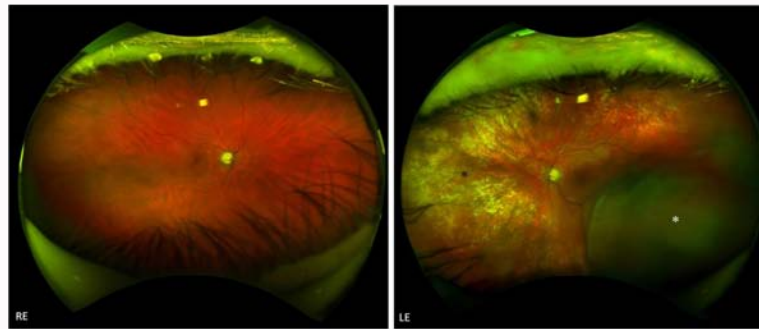

Figure 1: Ocular lymphomas are either intraocular or adnexal lymphoma. Intraocular lymphoma is divided in 3 categories: Primary vitreoretinal, primary uveal and secondary to a systemic disease.

Figure 2: PVRL complicated by an exudative retinal detachment. The Right Eye (RE) is not affected. The Left Eye (LE) photography shows inferotemporal retinal detachment (white asterisk) and numerous peripheral pigmentary alterations, as scars of retinal infiltrates (black asterisk).

Diagnosis

Ocular samples are mandatory for diagnosis. When a PVRL is suspected, cytokine levels can be measured on aqueous humor or vitreous tap as screening method. Interleukin-10 (IL-10) is an immunomodulatory cytokine secreted by malignant lymphocytes and its level in the eye is related to the density of neoplastic infiltration in the vitreous. Interleukin-6 (IL-6) is secreted in inflammatory non neoplastic pathologies. A IL-10/IL-6 ratio superior to 1 is highly suggestive of intraocular lymphoma and can be used as screening method; the use of a ratio helps part with dilution errors [5,16]. There is however a variation amongst IL-10 expression (for example in sub-retinal lymphoma) and IL-10 can be expressed in acute retinal necrosis or ocular toxoplasmosis [11,14]. Absolute threshold values in aqueous and vitreous have also been determined by Cassoux et al. [26]. Cytokine levels in aqueous or vitreous can be used as diagnosis criteria when used in ISOLD score, which is the result of a mathematical algorithm that link interleukin levels to the probability of having PVRL. The score defines two certainty categories with more than 99% probability of having or not having PVRL. The confidence interval is 92%. The remnant 8% "grey zone" can then be classified in favor or not of PVRL [27,28]. This is summarized in Table 1.

Diagnostic pars plana vitrectomy is now the gold standard. Low cut speed helps preserve the integrity of the sample. Valved trocars and sutures help prevent local dissemination through the sclerotomies [3,12]. Pure and diluted vitreous is sampled and must be processed as fast as possible to the laboratory (less than 2 h) and to a specialized pathologist [18]. Even when all recommendations are respected, sensitivity is low; if clinical suspicion is strong and first vitreous sample negative, a contralateral vitreous biopsy should be performed [3]. Cytology is the gold standard, showing tumoral cells with high nucleus to cytoplasm ratio, nuclear abnormalities, numerous nucleoli, and granular chromatin [12,21]. Sensitivity is low (45% to 60%) because of the paucicellularity of the samples, the frailty of tumoral cells, the cytotoxic effect of corticosteroids on cellular membranes (they must be stopped at least 2 weeks before biopsy), and the reactive T-cell environment [5,6,12,18]. Flow cytometry and immunohistochemistry are used to show monoclonality [11,12]. Polymerase Chain Reaction (PCR) shows immunoglobulin gene rearrangements and monoclonal populations [5]. IgH rearrangement is often observed in B-cell lymphomas [12]. MYD88 mutation in found 62% to 88% of PVRL [12]. None of these analyses have a 100% sensitivity. According to the French LOC Network recommendations, final diagnosis needs two criteria amongst those following: Typical ophthalmic signs, cytologic proof, immunohistochemical proof, molecular biology proof, positive ISOLD score [18].
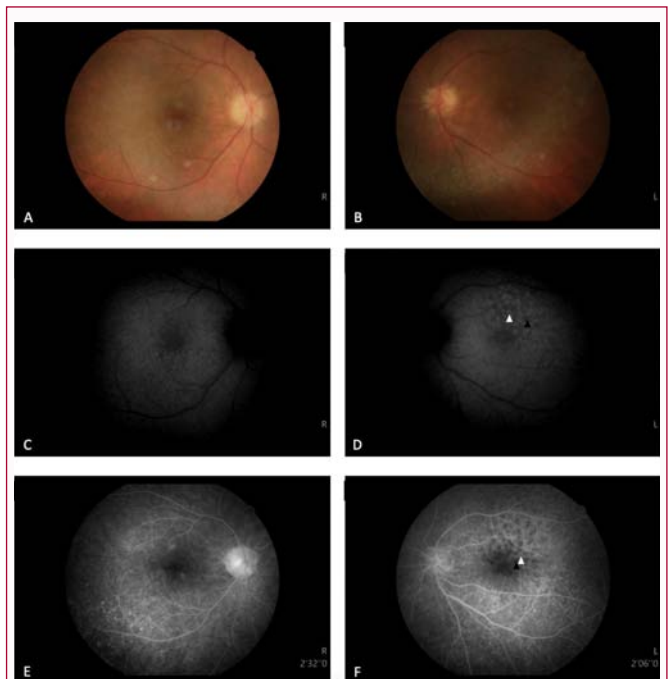

Figure 3: Multimodal imaging of the same patient with bilateral PVRL. Color fundus photography (A, B) shows discrete retinal infiltrates. Fundus autofluorescence (C, D) shows hyperautofluorescent spots (white arrow) surrounded by retinal pigment epithelium atrophy (black arrow). Fluorescein angiography (D, E) shows typical leopard spot retinopathy characterized by an alternation of hyperreflective (white arrow) and hyporeflective (black arrow) foci.

Once diagnosis is made, systemic extension must be ruled out in collaboration with hematologists, using at least brain MRI, PET-CT and lumbar puncture. Testicular ultrasonography and medullary biopsy are sometimes recommended [29].

Treatment

Local treatment comprises Intravitreal Injections (IVT) and radiotherapy. Intravitreal molecules commonly used are methotrexate (antimetabolite) or rituximab (anti-CD20). Anterior chamber tap before each injection helps reduce intraocular pressure and the risk of reflux by punction site, and can be used to monitor interleukin levels [18]. Methotrexate IVT 0.4 mg/0.1 mL lead to local remission after an average of 6.4 injections and the disease control in 95% of eyes after an average of 13 injections [30]. Frequency of injections is usually twice a week during induction phase (4 weeks or until clinical remission), then weekly during consolidation phase (4 to 8 weeks),

Table 1: Interleukin measures in intraocular fluid can be used as screening or diagnosis criteria.

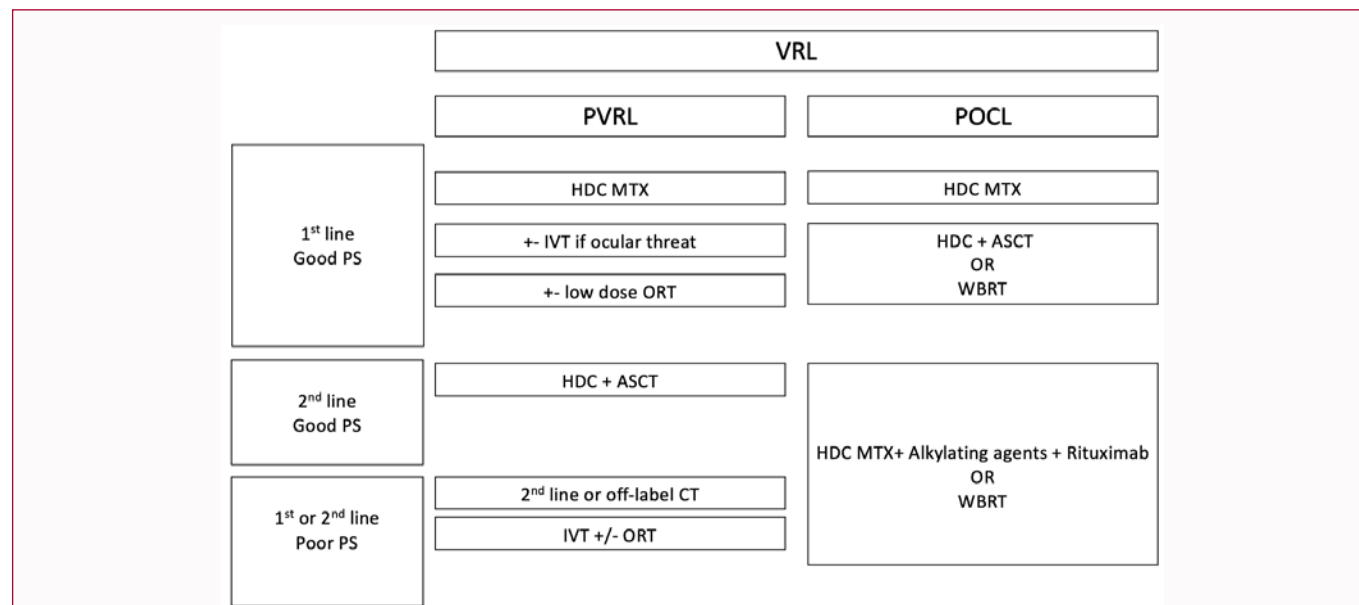|	Purpose	Threshold values	Sensitivity	Specificity
IL-10: IL-6 Ratio	Screening	>1	88% (5)	85% (5)
IL10 abs. value aqueous	Screening	>50 pg/mL	89% (25)	93% (25)
IL-10 abs. value vitreous		>400 pg/mL	80% (25)	99% (25)
ISOLD score	Diagnosis	> +4.6 < -4.6	93% (26)	95% (26)

Figure 4: Simplified treatment algorithm based on the latest French LOC Network recommendations.
VRL: Vitreoretinal Lymphoma; PVRL: Primary Vitreoretinal Lymphoma; POCL: Primary Oculocerebral Lymphoma; PS: Performance Status; CT: Chemotherapy; HDC: High-Dose Chemotherapy; MTX: Methotrexate; ASCT: Autologous Stem Cell Transplantation; WBRT: Whole Brain Radiotherapy; ORT: Ocular Radiotherapy; IVT: Intra-Vitreal Injection

then monthly during 9 to 12 months. The most frequent secondary effect is corneal epitheliopathy, which can be treated with 0,003% folinic acid drops [6]. Rituximab IVT 1 mg/0.1 mL is used as second line in case of corneal epitheliopathy or methotrexate resistance [31]. It leads to remission in 64.6% of eyes after an average of 4 injections, but there is a 50% risk of recurrence [5]. Secondary effect includes reversible uveitis [6]. Low dose (30 Gy to 40 Gy) Ocular Radiotherapy (ORT) is suggested in case of bilateral disease as rescue strategy [6,3,32]. It leads to many complications with doses as low as 20 Gy: Radiation retinopathy, intravitreal hemorrhage, ocular dry syndrome, conjunctivitis, neovascular glaucoma, optic nerve atrophy, cataract [3,12]. Local recurrence rate is high and treatment cannot be repeated [14,31]. Currently, some centers propose very low dose (24 Gy) fractionated radiation therapy as consolidation after successful systemic chemotherapy [18].

Systemic therapy is based on chemotherapies like those used in PCNSL. High-dose methotrexate is the main agent and its ability to penetrate through the ocular-blood barrier and blood-brain barrier is proven since the 90's [5,18,31]. It's often combined to other molecules as rituximab, cytarabine, etoposide [3]. Second line chemotherapies are temozolomide, lenalidomide, ibrutinib [6,18]. Ibrutinib is an oral chemotherapy, targets the MYD88 pathway and is associated with 80% therapeutic answer in DLBCL [3,14]. Autologous stem cell graft can be proposed as second line therapy if performance status is good [6].

Treatment of POCL makes consensus: It is the same as PCNSL. Induction protocol uses high-dose methotrexate chemotherapy and consolidation protocol uses autologous stem cell graft. Local treatment is used only when ocular disease persists after systemic chemotherapy [14,29]. On the contrary, PVRL treatment does not make consensus, especially if PVRL is unilateral: Should we treat locally, systemically or both? The benefit of systemic over local treatment would be to treat subclinical disease in order to delay CNS infiltration; however, it hasn't been proven in multicentric randomized trial [5,18]. The French LOC Network proposes an algorithm based on existing proof and personal expertise, it is resumed in Figure 4 [6,18,33]. First line treatment is systemic chemotherapy as in PCNL and POCL. In case of resistance or recurrence, autologous stem cell graft is proposed in healthy and less than 70 years old patients; while second line chemotherapies and local treatments are proposed in elderly comorbid patients. Local treatment is used if there is an ocular threat, in case of residual local disease after induction chemotherapy, contraindication to systemic chemotherapy, second line palliative treatment or if there is high clinical suspicion without histological proof [14].

Follow-up of therapeutic response rely on subjective ophthalmic examination; there should be close follow-up until the end of consolidation at least [6,12,18,33]. IL-10 levels in aqueous can be used to monitor therapeutic response (after induction, after consolidation and if recurrence is suspected) but it is not highly related to remission or overall survival [18]. There is no study defining the frequency of brain MRI follow-up, they can be repeated quarterly to yearly depending on the centers [18]. Prognosis remains poor with frequent progression to brain involvement and median survival is between 58 and 75 months [18].
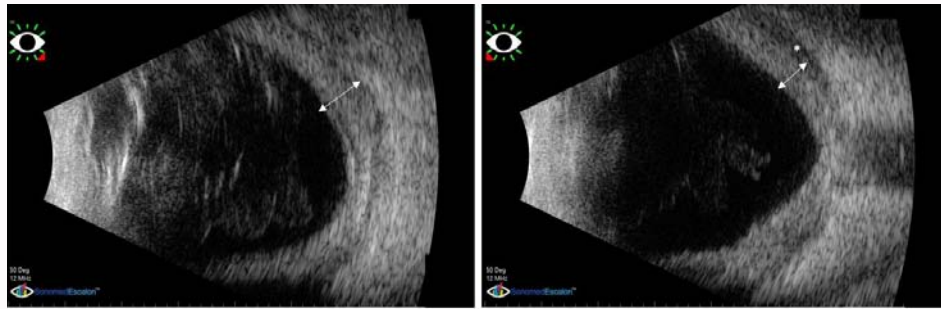
Figure 5: B-mode ultrasound image of the eyes of a patient with mixed uveal and episcleral lymphoma. White arrows show the massive thickening of choroidal and episcleral tissues bilaterally, accompanied by posterior hypoechoic fluid (white asterisk). This aspect and the clinical presentation looked like posterior scleritis with choroidal folds at first. The histologic analysis showed episcleral infiltration towards the choroid. This points out clinical and histological similarities between uveal and adnexal lymphomas.

Uveal Lymphomas

Primary uveal lymphoma is rare and usually low-grade small B-cell lymphomas. They were formerly named benign reactional lymphoid hyperplasia or uveal pseudotumor. Systemic involvement is rare, and prognosis is good [7,9,34].

Clinical features

Choroidal involvement is the most frequent [7], affects middle-aged men [16], and is bilateral in 54% of cases [7]. Symptoms are recurrent blurred vision or metamorphopsia. Clinical signs are yellow-white choroidal mass syndrome, exudative retinal detachment, ocular hypertension, proptosis, chorioretinal folds, and optic disc edema. Vitreous usually remains clear [7,11,34]. Differential diagnoses are uveal melanoma, uveal effusion syndrome, posterior scleritis, posterior uveitis (such as Vogt-Koyanagi-Harada syndrome, bilateral diffuse uveal melanocytic proliferation) [7,34-36]. Uveal involvement can extend locally to episclera, subconjunctival space and the orbit: This points out again the clinical and histological correlation between adnexal and uveal lymphomas as mentioned before [7,10,34].

Diagnosis

B-mode ultrasound and OCT show irregular thickening of the choroid (Figure 5); it's also noticeable as hyperintense signal on T1-sequence orbit MRI [7,37]. Indocyanine green angiography shows masking effect of tumor cells infiltrates. Ocular samples (transvitreous, transscleral or chorioretinal biopsies) for histological proof can confirm diagnosis, but it is not always achievable. Immunohistochemical analysis is essential to differentiate reactional inflammation from low grade lymphoma [34].

Treatment

As clinical course is indolent, treatment is less aggressive than in PVRL. In case of unilateral involvement, ocular external beam radiotherapy can be proposed. In case of bilateral or systemic involvement, systemic chemotherapies or biologic agents (chlorambucil, rituximab…) can be proposed as first line treatment, and immunotherapies as second line [7,37,38].

Other uveal lymphoma

Ciliary lymphoma is extremely rare. We quote one case series in China that reported 8 cases in which Ultrasound Biomicrosopy (UBM) showed annular continuous solid infiltration of low intern reflectivity in 100% of cases [39]. Iris lymphoma is also extremely rare and manifests as iris infiltration, heterochromia, anterior uveitis, rubeosis and secondary glaucoma [16].

Conclusion

Intraocular lymphoma can manifest as a masquerade syndrome of uveitis and its early recognition is important for oncologic purposes. PVRL is the most frequent and has poor prognosis. It should be considered as differential diagnosis in case of chronic vitritis without typical signs of intermediate uveitis and incomplete answer to corticotherapy in a patient over 50 years old. Ocular samples are mandatory for diagnosis and vitreous biopsy in is the gold standard. The quality of samples and the expertise of pathologist are of outmost importance to improve diagnosis sensitivity. Treatment needs close collaboration between oncologists and ophthalmologists, and we lack objective measures to monitor therapeutic response. The choice of therapeutic options needs to be discussed with the patient and should be held by ophthalmic centers with high expertise in ocular oncology. On the other hand, uveal lymphoma is less frequent, mostly choroidal, primary with low and good prognosis, or secondary with poor prognosis. It can also manifest as masquerade syndromes of uveal pathologies.

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