PRIMARY VITREORETINAL LYMPHOMA: AN OPHTHALMOLOGIST PERSPECTIVE ON DIAGNOSIS AND TREATMENT

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Primary vitreoretinal lymphoma (PVRL) is a rare subset of central nervous system lymphoma occurring primarily in the vitreous and retina. Often presenting as a masquerade syndrome mimicking infectious or non-infectious uveitis, PVRL presents a diagnostic and therapeutic challenge. A vitreal or retinal biopsy is essential for diagnosis. This paper reviews recent advances and updates in the diagnosis and treatment of PVRL with a focus on intravitreal chemotherapy. Current diagnostic techniques for PVRL are demanding and detailed clinical history, examination, ocular and central nervous system imaging with immunohistochemistry, flow cytometry, molecular and genetic analysis are needed. In the last few years, local intravitreal treatment in cases with isolated PVRL is the topic of many published papers, however, the number of patients involved is small and treatment recommendations are not standardized and unique.

Key words: **lymphoma, masquerade, intraocular, extranodal, intravitreal treatment, local chemotherapy**

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INTRODUCTION

Primary vitreoretinal lymphoma (PVRL) is a rare, primary intraocular disease of the vitreous and neuroretina. It is the most frequent intraocular lymphoma subtype, after primary uveal lymphoma and systemic metastatic retinal lymphomas (1). It represents a subset of central nervous system (CNS) lymphoma (2, 3). Prognosis is generally poor due to late disease recognition and poor treatment response with secondary CNS involvement at presentation in 16%-50% (4, 5). Secondary involvement of CNS is reported to occur in up to 53.8% (6) of cases. Advancements in treatment in recent years have shown promising results with great local control and prolongation of the interval to CNS spread, with reported 5-year survival rate of 71% with proper management (5). Randomized studies are lacking due to the rarity of the disease and consequently, the protocols and clear guidelines for the treatment of PVRL are very diversely reported in the literature. The use of multimodal therapy combining systemic chemotherapy with radiotherapy and intravitreal therapy has evolved and has improved the disease prognosis. In recent years, ever more importance is given to local, intravitreal chemotherapy for patients with both isolated PVRL and PVRL with known CNS involvement, as it provides good local control of the disease and even prolongs the interval to CNS involvement (5). Intravitreal methotrexate and rituximab have been routinely used in practice with the addition of novel therapies (7-16).

CLINICAL PRESENTATION

Clinical features of PVRL are one of the masquerade syndrome (17). The mean duration of symptoms before reaching the correct diagnosis has been reported as 6 months (18). PVRL can occur at any age, but mostly affects patients from the third to eighth decade of life (4), with median age at diagnosis of 64 (range 48-87) years (7).

In 60%-90% of cases, there is bilateral ocular involvement, even if the disease clinically seems to be unilateral (18, 19). PVRL is often presenting itself as chronic posterior uveitis in the elderly (20, 21), with symptoms of blurred vision in 40%-50%, floaters in 20%-25% and decreased visual acuity in 25%-30% of patients (18). Anterior eye segment findings are inconclusive, there is mild conjunctival injection and mostly no posterior synechiae (21); some have stellate keratic precipitates and cells in the anterior chamber (22, 23), and rare cases present with infiltration of the angle or pseudohypopyon (23). In PVRL, there is typically vitritis with clumps, sheets or strands of cells present in the vitreous, and creamy lesions with orange yellow infiltrates on the retina, giving a typical look of leopard skin (24-26). In up to 40% of patients (27, 28), PVRL can also mimic choroiditis and vasculitis with perivascular infiltrates, rarely PVRL can present with optic nerve infiltration (29-33). Cystoid macular edema (CME) is rare and thus visual acuity is often relatively preserved (34).

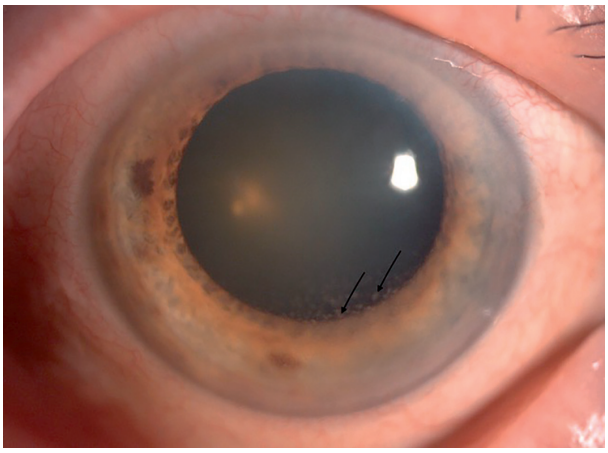

Figure 1. *Anterior segment of PVRL patient: right eye with mild conjunctival injection, no posterior synechiae, stellate keratic precipitates (black arrows), cells in anterior chamber are not visible.*

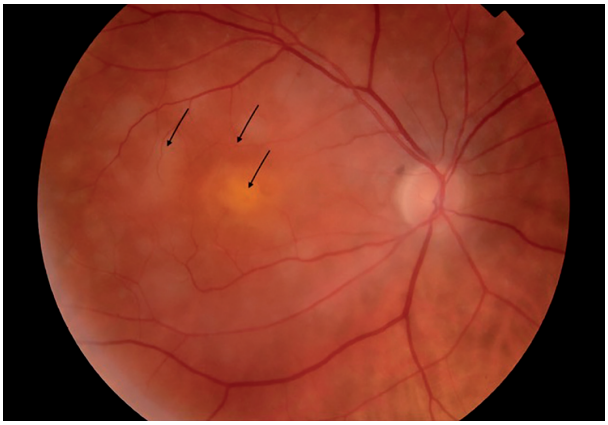

Figure 2. *Retinal infiltrates in PVRL patient: right eye with not completely clear fundus view because of cells in the vitreous (not visible); creamy lesions with orange yellow retinal (subretinal) infiltrates on the posterior pole are seen (black arrows).*

DIFFERENTIAL DIAGNOSIS

Since PVRL is a masquerade syndrome, there is a wide spectrum of differential diagnoses, covering infectious and noninfectious uveitis, such as all forms of posterior or intermediate uveitis or panuveitis. Differential diagnosis can also be extended to neoplasms, metastatic cancers, and amelanotic melanoma (4, 35, 36).

PATHOLOGY AND ETIOPATHOGENESIS

Most PVRL cases are diffuse large B-cell lymphomas (37). Since the eye is an immune-privileged site in which normal immune mediated inflammation and recognition of foreign antigens are inactive, some speculative theories about the etiopathogenesis of PVRL have been proposed, i.e., the cause of PVRL could either be the attraction of malignant B-cells to intraocular space or intraocular malignant transformation of B-cells (37). Cytokine analyses in primary central nervous system lymphoma (PCNSL) have shown increased production of cytokines that promote chemotaxis and prolong B-cell survival (CXCL12 and CXCL13, IL-10) and an increase in the expression of their receptors (CXCR4 and CXCR5) (38-42). Chan (42) hypothesizes that there is a hematologic spread of neoplastic cells, i.e., lymphoma cells are attracted to the retinal pigment epithelium (RPE) from the choroidal circulation. Ligands, B-lymphocyte chemoattractant (BLC) and stromal cell-derived factor-1 (SDF-1), were found only in the RPE, and B-cell chemokine receptors (CXCR4 and 5) were found on lymphoma cells. Thus, B-cell chemokines may be involved in the pathogenesis of primary intraocular lymphoma. Some authors associate the disease with infectious agents,

predominantly Epstein-Barr virus (EBV), human herpes virus-8 (HHV-8) (43) and less frequent *Toxoplasma gondii* (44), which can trigger antigen-driven B-cell proliferation that becomes monoclonal with time with neoplastic transformation and cause lymphoma. The infectious theory is partly supported by finding EBV in AIDS patients with PCNLS (45). There is also dysregulation of IL-10 production, i.e., an increase in IL-10 levels downregulates the immune response to malignant cells and control over cellular proliferation. On the other hand, increased levels of IL-10 enhance B-cell survival, proliferation and antibody production, and lead to increased production of potentially malignant cells (46, 47).

DIAGNOSIS

Primary vitreoretinal lymphoma is part of the well-named masquerade syndrome, e.g., an insidious onset, initial response to steroids, and delayed diagnosis due in part to the common prolonged and indiscriminate use of steroids are common (53). Besides the clinical picture described, ocular and CNS imaging are the key features in the diagnosis of the disease.

OCULAR IMAGING

Ocular imaging and imaging of CNS are the key features in the diagnosis of the disease. In optic coherence tomography (OCT), nodular or band hyperreflective lesions/spots in the RPE layer are seen in 43% of PVRL patients (48), as well as damage to the RPE, disruption of the inner/outer segment layers of photoreceptors (49). Reduced foveal thickness is present compared to uveitis cases (4), and the absence of cystoid macular edema is useful to confirm suspicion of PVRL.

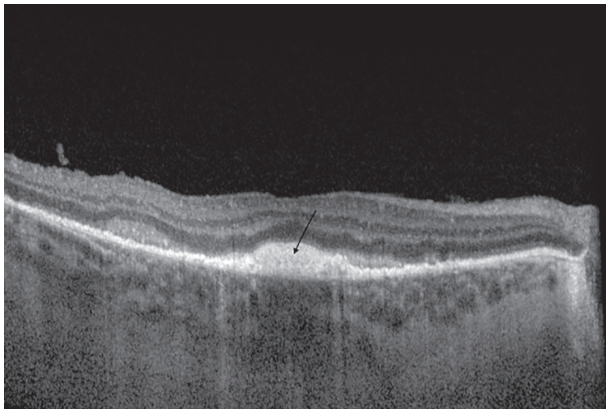

Figure 3. *Optical coherence tomography of PVRL patient: right eye, nodular hyper-reflective deposits throughout the macula and subfoveolarly are also seen (black arrow).*

Fundus autofluorescence (FAF) is useful in diagnosis and follow-up. Hypoautofluorescent areas correspond to RPE atrophy or lymphoma cells above the RPE, while on hyperfluorescent spots, there is overlapping of PVRL and RPE cells. The treatment effect can be seen on FAF; hyperautofluorescent spots turned to hypoautofluorescent after intravitreal methotrexate treatment (48, 50). There is a new report confirming the usefulness of FAF; a small study conducted by Casady (48) showed that granular autofluorescence patterns can be associated with active disease although the negative predictive value was low. According to this study, FAF granularity was also the main reason for clinical suspicion where there was no 'leopard skin' pattern on fluorescein angiography (FA) or indocyanine green angiography (ICG).

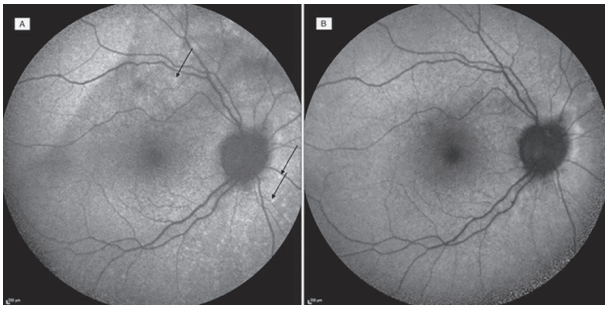

Figure 4. *Fundus autofluorescence before and after treatment: right eye, hyperautofluorescent spots representing active disease (A, black arrows), regressing after treatment with intravitreal methotrexate, B).*

The most typical feature on FA are extensive RPE changes shown as hypofluorescent round spots with a 'leopard-spot' appearance (27, 34), and also granularity, blockage and late staining. Cystoid macular edema (CME) and perivascular staining are rare (34). Only 2% of the 44 patients in the study by Cassoux had CME (51). RPE detachment and punctate hyperfluorescent lesion as window defects can also be seen (27). ICG shows small hypofluorescent lesions in early phase, which are less apparent in late phases and can be seen better on FA. FA and ICG have a positive predictive value of 89% and negative predictive value of 85% (4, 27).

Abnormal ultrasonographic findings were found in all patients in the study by Ursea (52); most commonly there was vitreous debris, choroidal-scleral thickening, widening of the optic nerve, elevated chorioretinal lesions, and retinal detachment. B-scan ultrasound is a useful diagnostic tool, but it is often nonspecific.

NEUROIMAGING

Primary vitreoretinal lymphoma is closely related to PCNSL and it is therefore imperative to evaluate CNS with magnetic resonance imaging (MRI) (53). According to the literature, 42%-92% of PVRL patients present with intracranial lymphoma within less than 2.5 years (4, 23, 51, 54). The preferred methods in MRI of the cranium are fluid-attenuated inversion recovery (FLAIR) and T1-weighted sequences before and after contrast injection (55).

TISSUE BIOPSY AND MOLECULAR ANALYSES

Definitive diagnosis of PVRL is made by detection of malignant lymphoid cells in the retina, vitreous and/or optic nerve (56), which must be done at any cost before deciding to start treatment (57). The diagnosis could remain challenging due to a limited sample volume, low cellularity of vitreous fluid samples, and extreme fragility of lymphoma cells in the vitreous. Discontinuation of steroids several weeks before vitrectomy, good communication and collaboration between the ophthalmologist and the cytologist/pathologist trained in handling vitreous samples, and immediate analysis of both pure and diluted vitreous samples are critical for success (58).

An adjunct to diagnosis is the measurement of specific cytokines in aqueous and vitreous (59). An IL-10/IL-6 ratio >1 or elevated IL-10 level in an aqueous or vitreous specimen is suggestive of PVRL; however, the precise cut-off of IL-10 concentration or IL-10/IL-6 ratio may differ between laboratories. A recent study on 103 uveitis samples showed cut-off of 65 pg/mL for IL-10 and IL-6 30 pg/mL for IL-6 in the vitreous and aqueous humor, and was correlated with 93% and 78% sensitivity and 100% and 97% specificity, respectively (61, 63).

Morphological evidence for PVRL is characterized by atypical lymphoid cells (49). Histologically, according to the WHO classification, PVRL is mostly a high-grade malignant non-Hodgkin's lymphoma, and in most cases a diffuse large B-cell lymphoma (56). Phenotyping of cell surface markers is useful for identification of lymphomatous cells, especially in cases where cytology is not sufficient (62-64). Supportive to the diagnosis of PVRL is the monoclonality of B-cell population (CD19, CD20 or CD22 B-cell markers) with restricted expression of either kappa or lambda or T-cell population (CD3, CD4) (66). To identify the clonal population of B and T lymphocytes, immunoglobulin heavy chain (IgH) gene sequencing, particularly in the third complementarity-determining region (CDR3), have been used (20). PCR studies suggest that PVRL cells 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 (66). Flow cytometry is used for profiling of larger panels of different cell surface markers simultaneously to help differentiate uveitis from lymphoma. A kappa to lambda ratio of >3 or <0.6 is a marker of clonality. The ratio in inflammatory reactions is close to 1 (67).

The gold standard in diagnosis is vitreous or retinal biopsy which proves malignant cells in the vitreous and/or retina. Several disadvantages such as the vitreous size sample, low cellularity of the sample and high level of necrosis in the tumor make the diagnosis difficult. Only cytologically confirmed PVRL can be treated as such. Pars plana vitrectomy is performed to obtain sufficient vitreous specimen (68). If the patient is on corticosteroid treatment, this should be stopped two weeks before the procedure (69). If there is a need for retinal biopsy with retinectomy or fine needle aspiration, samples are taken from the retina, near to choriocapillaris, where viable lymphoma cells are most likely to be found (70). Lymphoma cells are highly sensitive to environmental stress, and it is of utmost importance that vitrectomy is performed by an experienced surgeon; it is also very important that the samples be handled gently to prevent cell degeneration. Lymphoma cells undergo morphological degradation within 60 min and if transport time exceeds this, an appropriate preservative should be used (69). During pars plana vitrectomy, vitreous cells are taken before saline infusion and after as much as possible. Diluted and undiluted samples are immediately sent to cytology. In this case, the negative predictive value is high, around 60% (71). The rate of success increases with repeated vitrectomies, retinal biopsies and with close collaboration between ophthalmologists and pathologists (72, 73).

Next-generation genetic sequencing is another aid in diagnosis. MYD88 L265P mutation, typical of hematologic B-cell malignancies, is an oncogenic mutation (74) and detection of this mutation provides definitive evidence for a malignant neoplasm, i.e., PVRL (75). In the last few years, there were continuous literature reports on MYD88 mutations in PCNSL for detection of L265P mutations (74, 76-79). Techniques used for detection of the above-mentioned mutation are different. In the study by Cani (77), the targeted next-generation sequencing (NGS) technique was shown to be a promising method in intraocular liquid biopsies; diluted samples contained enough genomic DNA for analysis. In the study by Hiemicke (75), a sensitive droplet digital PCR (ddPCR) was used to detect MYD88 L265P mutation in the vitreous and aqueous humor in patients with VRL and uveitis. The mutation was

detected in 74% of VRL patients in the aqueous humor and in the vitreous, and none in uveitis patients. In the vitreous fluid and aqueous humor (AqH), the MYD88 ddPCR test showed a positive predictive value and specificity of 100%, sensitivity of 75% in the vitreous fluid and 67% in AqH. After treatment, the mutation was no longer detectable in any of the ocular fluids.

When PCNSL is suspected, lumbar puncture should be performed. Up to 25% of patients with identifiable lesions on MRI have positive cerebrospinal fluid (CSF) cytology (19, 80). Stereotactic brain biopsy is performed if there are suspicious brain lesions on MRI (81).

To make definitive diagnosis of PVRL, a multidisciplinary approach and good collaboration are key features for success. Cell samples from the above-mentioned tissues are sent to pathologists who perform cytopathologic evaluation, immunocytochemistry, and flow cytometry.

TREATMENT PANEL

The approach to treatment is multidisciplinary and includes systemic therapy, local therapy in terms of radiotherapy, and chemotherapy. There is no definitive consensus on the treatment of PVRL, especially isolated intraocular disease with no CNS involvement. Treatment is focused on intraocular and retinal disease in two ways, i.e., to restore the patient's vision and to decrease the incidence of CNS relapses (20, 53). The main two approaches are local therapy and systemic therapy with local therapy. The basic treatment algorithm is shown in Figure 5.

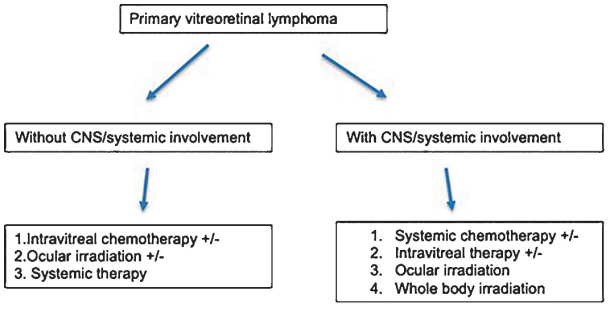

Figure 5. *Treatment of primary vitreoretinal lymphoma (adapted from European Association of Neuro-Oncology guidelines for the treatment of PCNSL) (20). The above-mentioned approaches are embedded with +/- signs for local +/- systemic treatment in isolated PVRL or vice versa in PVRL with CNS/systemic involvement.*

Primary vitreoretinal lymphoma initially partially responds to corticosteroid treatment as corticosteroids have an antineoplastic effect (82) and patients are on topical and systemic corticosteroid treatment for presumed uveitis/vitritis before the diagnosis of intraocular lymphoma has been made. All PVRL patients who received steroids showed either a transient response or no response that could point to the diagnosis.

Local radiotherapy

Doses between 30 and 36 Gy, 1.5-2.0 Gy fractions are recently administered in ocular irradiation (83). All these doses can cause complications such as radiation retinopathy, dry eye syndrome, conjunctivitis, punctate epithelial erosions, or cataract (22, 84). Radiation retinopathy can be caused even with doses less than 20 Gy, as it was shown in the study by Kaushik (85). However, the rate of local recurrence is 7%-56% (86, 87) and treatment has limited repeatability (89).

Ocular-intravitreal chemotherapy

Intravitreal chemotherapy is now the mainstay of the treatment of PVRL. Its role is intensely researched especially in patients with PVRL without CNS involvement, where there is much controversy in different approaches since there is no large and prospective randomized control trial available on that topic. In 2007, an International Primary Nervous Central System Lymphoma Collaborative Group retrospectively reviewed 83 primary intraocular lymphoma patients without CNS involvement but including 9 patients with positive CSF cytology from 16 centers (19). They compared two general treatment strategies, focused intraocular (methotrexate, radiation, and combination) and general with or without focused intraocular therapy. They did not reveal any significant difference between these two strategies in terms of the site of relapse, progression free survival or overall survival. That implicates that focused intraocular therapy for primary intraocular lymphoma with strict follow up may be appropriate. Starting with systemic chemotherapy or whole brain radiotherapy (WBRT) would be reserved for tumor progression. The same International Primary CNS Collaborative Group retrospectively reviewed 221 patients with PCNSL and VRL a year later from the same 16 centers (89). In those 221 patients, the same patients from previous study (19) with isolated primary intraocular lymphoma were included, others had brain lymphoma with ocular dissemination. The study found out that adding focused therapy, as defined above in previous study (19), resulted in prolonged disease control but did not impact survival or risk of recurrent ocular lymphoma. In 2015, a multicenter study on PVRL treatment strategies involving 17 referral ophthalmologic centers in Europe included 78 PVRL patients without CNS involvement at presentation (67). It showed that the use of systemic chemotherapy was not proven to prevent

CNSL progression, it was similar as in patients receiving local ocular treatment only. In 2018, Abu Samra published a 10-year review of tertiary referral center records of 51 eyes of 26 ocular lymphoma patients with minimum 6-month follow up (72). He divided patients into 3 groups, as follows: patients with VRL with CNS involvement, patients with VRL lymphoma and systemic lymphoma, and patients with PVRL without CNS involvement. Patients with PVRL were treated with a combination of intravitreal methotrexate and rituximab, while patients with concomitant CNS or systemic lymphoma were treated additionally with systemic chemotherapy or radiotherapy. All patients had resolution of vitreoretinal lesions after treatment. After 5-year follow up, all patients from all groups were still alive and in remission, and after 10 years only 3 patients died. The report suggests that PVRL without CNS involvement can be managed with local measures (intravitreal methotrexate or rituximab or local irradiation). With this approach, toxicity of systemic treatment is reduced. The same recommendation to avoid toxicity with local treatment was stated by the International Primary CNS Collaborative Group (IPCG) (19).

There are some studies not supportive of the above-mentioned ones, however, they are not multicenter and include less patients. Castellino (91) proposed a different treatment approach; they analyzed data of a single center over a 28-year period. They had three groups of patients, i.e., isolated PVRL, concurrent intraocular and CNS lymphoma or systemic lymphoma, and secondary VRL. The analysis showed that combined systemic and intraocular therapy for PVRL resulted in higher median of failure-free survival and CNS relapse-free survival, concluding that VRL required combined systemic and intraocular chemotherapy to prevent CNS progression. The study by Klimova (5) from 2016 included 20 patients, i.e., 10 with PVRL only and 10 with PCNSL with VRL plus 53 patients with primary CNS lymphoma without intraocular involvement. The reported 5-year survival rate was 71%. A significantly longer 5-year survival rate of 89% was recorded in patients with PVRL without CNS involvement comparing to survival of patients with PCNSL with vitreoretinal involvement (58%) and PCNSL without vitreoretinal involvement (34%).

Possibilities of intravitreal treatment

The two most common agents used for intravitreal treatment are methotrexate and rituximab. Methotrexate is the first intravitreal treatment option for PVRL patients since the study by Frenkel (90) demonstrated that there was no intraocular recurrence in 26 patients. On the other hand, with intravitreal rituximab the disease recurred in approximately half of the eyes (6).

INTRAVITREAL METHOTREXATE

Methotrexate is an antimetabolite, a folate antagonist. It inhibits cell growth and proliferation by depleting the pool of reduced folates or tetrahydrofolates; it is a cytotoxic drug (92). Besides being fundamental therapy for the treatment of non-Hodgkin's lymphoma, methotrexate is also used in ophthalmology, i.e., it is one of the most widely used immunosuppressants for uveitis patients who need steroid-sparing treatment. The first published papers about intravitreal treatment of intraocular lymphoma with methotrexate date back to 1995 (93).

In 1997, Fishburne (94) treated 7 eyes of 4 patients with a 14-month course with intravitreal methotrexate and systemic therapy, and all treated eyes reached remission with no serious ocular side effects, with median follow up of 14 months. Later, they published a larger retrospective case series (95) including 26 eyes of 16 HIV-negative patients, where they evaluated the safety and efficacy of intravitreal methotrexate. All patients had PCNSL with ocular involvement. Two patients with isolated PVRL received only intravitreal methotrexate without systemic therapy. Clinical remission was reached by 100% of eyes. In 3 patients who relapsed during a median of 18-month follow up, second clinical remission was achieved with the prolonged course of intravitreal chemotherapy. Six out of 16 patients died due to intracranial progression of the disease, however, with no signs of intraocular tumor.

In 2008, Frenkel reported results of a 10-year retrospective study (91); they treated 44 eyes in 26 patients. Clinical remission was achieved in all patients, and no intraocular recurrence was found. In 2008, another study from Japan was published (96). These authors treated 10 eyes of 6 patients, with 3 patients without CNS involvement after at least 30 months. All patients also received systemic therapy from the start. Nine eyes achieved remission, with the only side effect of corneal epitheliopathy and one cataract progression. In 2012, a retrospective chart review was published from a longitudinal study. The authors observed changing approaches in the treatment of vitreoretinal lymphoma during 17 years at one center (97). Median follow up was 33.5 months. There were 12 eyes of 8 patients; 7 patients had CNS non-Hodgkin's lymphoma. Six eyes were treated with intravitreal methotrexate and none of the patients had recurrence of vitreoretinal lymphoma. A report by above-mentioned Samra (72) in 2016 showed remission of intraocular lymphoma in all 25 patients receiving intravitreal methotrexate and/or rituximab. The mean follow up was 56 months; at the mean follow up of 10 months, 3 patients showed recurrence of intraocular lymphoma and received further intravitreal methotrexate or rituximab and

resolved completely. Another two studies from China from 2016 (88, 98) evaluated effectiveness of intravitreal methotrexate, among other things. Altogether 29 patients achieved remission after intravitreal methotrexate treatment, some in combination with systemic treatment. Side effects of intravitreal methotrexate are well documented and encompass corneal epitheliopathy which is one of the most common side effects (95, 99). According to the studies by Smith (95) and Wei (94), it can reach up to 58%, then progression of cataract (37%-73%), maculopathy (42%), vitreous hemorrhage (8%), optic atrophy (4%), glaucoma (3%) and sterile endophthalmitis (10%). Corneal epitheliopathy can be resolved naturally when the once/twice weekly schedule regimen is omitted.

The dose of methotrexate used for intravitreal treatment is 400 μg/0.1 mL. This dose achieved local tumor control in relapsed PIOL, in ocular relapse of PCNLS, and as primary treatment in combination with systemic therapy (4, 93, 94, 100, 101). The time administration protocols are different; the ones proposed and used in our tertiary center are mostly intravitreal injections given twice weekly for 4 weeks, weekly for 8 weeks, and monthly for 9 months (4), which follows most of the literature recommendations (91, 94, 95).

With the studies mentioned showing high effectiveness in inducing ocular remission and re- remission after relapses, and the clear fact that even high dosage methotrexate intravenously does not reach tumoricidal levels within the vitreous (102), intravitreal methotrexate is now routinely used for the treatment of primary intravitreal lymphoma.

INTRAVITREAL RITUXIMAB

Intravitreal rituximab, a humanized monoclonal antibody, is often used in methotrexate resistant cases or to decrease the frequency of methotrexate injections, thus decreasing the severity of side effect. It targets CD 20 positive cells while sparing normal ocular tissue such as human stem cells, progenitor cells, and neurons (103). First use of intravitreal rituximab for intraocular lymphoma was described in 2007. It was used to treat 3 patients (5 eyes) successfully and it did not have any ocular toxicity (104). A report of a patient who relapsed after vitrectomy and intravitreal methotrexate for PVRL treatment with intravitreal rituximab was published in 2009 (105). Intravitreal rituximab was applied and showed promising results without toxicity for ocular structures at short term, however, the patient relapsed after 3 months of therapy with visual deterioration. Further efficacy of local therapy with rituximab was reported in 2012 in a group of 12 eyes of eight patients, seven of them with concomitant CNS lymphoma (97). Local therapy with EBRT (3 patients), intravitreal methotrexate (6 eyes) and intravitreal rituximab (2 eyes) was proven to efficiently control PVRL. After a median follow up of 33.5 months, VRL resolved in 7 eyes and persisted in 5 eyes. In 2012, a prospective study of 20 eyes of 13 female patients with CD20+PVRL was reported (6). The patients were treated only with monthly intravitreal rituximab due to intravitreal methotrexate side effects in the form of severe corneal epitheliopathy. Rituximab was administered for 4 consecutive months and then additional monthly injections were given. If the disease still appeared active, all patients had at least 1-year follow up interval after treatment. In 69% of patients, secondary CNS involvement occurred. In 2013, a series of 10 patients with PVRL, who were repeatedly treated with intravitreal rituximab or methotrexate, was reported and IL-10 levels and IL-10/IL-6 ratio in the vitreous and aqueous were recorded, as these have been found to be good markers of therapeutic response or recurrence of the disease (61). The largest and most relevant study of intravitreal rituximab for the treatment of vitreoretinal lymphoma was conducted by Larkin in 2014 (106). It was a multicenter retrospective study which collected 34 patients (48 eyes) from 12 centers. Sole treatment with rituximab ± methotrexate was given to 39.6% of eyes; 37.5% with rituximab only. Complete remission was achieved by 64.6% of 48 eyes treated with intravitreal rituximab. Fifteen of those patients received intravitreal treatment only and 53% of those eyes achieved complete remission. Lymphoma occurred in 23% of those eyes after a median follow up of 18 months. The study showed that intravitreal rituximab was not superior to intravitreal methotrexate alone in terms of preventing relapse, but the number of injections and keratopathy could be reduced. According to the cited studies, secondary VRL has been shown to be well controlled with injections of intravitreal rituximab combined with methotrexate and such local therapy is well tolerated and reduces the intraocular tumor load in addition to systemic chemotherapy (107, 108). Ocular PVRL relapses managed with intravitreal rituximab (due to complications of intravitreal methotrexate therapy) have shown to provide good local control of the disease without evidence for toxicity (109).

Treatment with intravitreal rituximab has often been reported to be safe without ocular toxicity (72, 105, 110). Intravitreal therapy presents a general risk of complications such as cataracts, vitreous hemorrhage, endophthalmitis, and retinal detachment (106, 111). Besides, there is a specific side effect of intravitreal rituximab treatment; a prospective interventional study of 13 patients with PVRL evaluated side effects of intravitreal rituximab therapy and 35% of patients had iridocyclitis with mutton-fat KPs, responsive to local

treatment with transient intraocular pressure elevations in 60%. No other significant ocular complications or systemic side effects were reported (6). In the study by Larkin (106), granulomatous anterior uveitis affected only 2.1% (1 eye) of the observed pool. There is a serious case report of side effects of intravitreal therapy with rituximab reported in terms of occlusive retinal vasculitis (109, 112). However, there are some literature reports of vascular side effects of systemic therapy with rituximab in the form of cutaneous vasculitides (113).

The dose of rituximab used for intravitreal treatment is consistent, i.e., 1 mg/0.1 mL but scheduling the intravitreal injections of rituximab is not uniform. In 2019, a group of 18 eyes of 9 patients with PRVL treated with intravitreal rituximab was reported (115). Patients were divided into two groups according to receiving intravitreal rituximab biweekly or monthly schedules. SD-OCT were analyzed at every visit and compared. Conclusion was that treatment frequency with intravitreal rituximab did not influence the rate of disappearance of activity signs.

OTHER PROMISING INTRAVITREAL AGENTS

There are published reports of novel treatments in animal models using FasL vesicles to activate innate immunity and terminate the eye immune privilege (8). The HA22 immunotoxin was used by Li and Pastan (9, 10). Recombinant proteins, immunotoxins are chimeric proteins composed of Fv portion of a monoclonal antibody, which ensures target specific killing, fused to a portion of a toxin. Some other monoclonal antibodies (efalizumab, alemtuzumab, daclizumab), which showed effectiveness in animal models, were also studied (11). However, there are no new clinical application studies following the publication of the above-listed trials. In 2020, a study on the treatment of relapsed or refractory PVRL was published with promising results; single-agent temozolomide produced encouraging results in a retrospective study of 21 patients, not all with the disease limited to the eye. The overall response rate was 81% (115). Two targeted therapies, i.e., lenalidomide single or combined with rituximab and ibrutinib, were used in phase I and phase II studies (16, 116, 117).

To conclude, the real efficacy of intravitreal panel treatment possibilities as the sole first-line treatment for PVRL as stated by Cassoux cannot be properly assessed because of the heterogeneity encountered in retrospective studies in terms of disease characteristics (initial PVRL or relapse, vitreoretinal involvement associated with PCNSL) and frequent association of systemic treatments (58).

AUTOLOGOUS STEM CELL TRANSPLANTATION

From 2001 to 2012, a number of articles were published using stem cell transplantation for PVRL treatment (118-121). Concerning CNLS with PVRL, there was only one publication describing stem cell transplantation for PVRL (118). The results can be promising, however, limited to refractory PVRL cases. There are a few other agents such as ibrutinib and pomalidomide (14, 15, 117) used in the treatment of PVRL and PCNLS. They have not been used in clinical practice after the above-mentioned publication.

PROGNOSIS

Primary vitreoretinal lymphoma has a poor prognosis. The available data and publications do not allow a conclusion whether the PVRL prophylactic systemic therapy is effective in preventing the progression of CNS involvement or prolonging CNS progression-free survival (123).

Prognosis is better with the isolated central nervous system or vitreoretinal involvement. The mortality rate is inconsistent because of the rarity of the disease, delayed diagnosis, and various treatment modalities (124). According to Freeman (125), the 5-year survival rate was 30%; later, it was found to be around 55% (118, 126) and in 2012, a multicenter study from Japan reported a 5-year survival rate of 61% (127). The study by Tsubota published this year showed that there could be some new prognostic markers of survival, the most important being low serum IgA which was associated with shorter survival (128). Although the study was small and differences were not statistically significant, lower serum IgA was noticed in patients with MYD88 mutation which is often present in PVRL patients (129, 130).

CONCLUSIONS

Diagnostic techniques and treatment possibilities have improved in primary vitreoretinal lymphoma, an important ocular masquerade syndrome that mostly occurs in the elderly population. Diagnostic challenges with a novel (non)invasive diagnostic approaches and techniques are presented in the paper. The literature review for the intravitreal treatment of specifically isolated PVRL revealed many inconsistencies regarding combination with systemic treatment in terms of preventing CNS progression. However, because of the evident effectiveness of intravitreal treatment, it is now the standard of treatment of PVRL. It achieves durable ocular remission with fewer side effects as com-

pared with systemic treatment. The best therapeutic approach is yet to be found. The only and appropriate patient care is based on close collaboration between ophthalmologists, pathologists, and oncologists.

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SAŽETAK

PRIMARNI VITREORETINALNI LIMFOM: STAV OFTALMOLOGA O DIJAGNOZI I LIJEČENJU

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Primarni vitreoretinalni limfom (PVRL) rijetka je podskupina limfoma središnjega živčanog sustava (SŽS) koja se javlja ponajprije u staklastom tijelu i retini. Često se predstavlja kao maskirani sindrom koji oponaša infektivni ili neinfektivni uveitis pa je dijagnostički i terapijski izazov. Biopsija vitreusa ili retine bitna je za dijagnozu. Ovaj rad prikazuje nedavna dostignuća i ažuriranja u dijagnostici i liječenju PVRL s naglaskom na intravitrealnu kemoterapiju. Suvremene dijagnostičke tehnike za PVRL su zahtjevne. Potrebna je detaljna klinička anamneza, pregled, očna i SŽS slika s imunohistokemijom, protočna citometrija, molekularna i genetska analiza. Posljednjih nekoliko godina lokalno intravitrealno liječenje u slučajevima s izoliranim PVRL tema je brojnih objavljenih radova. Međutim, broj uključenih pacijenata je malen, a preporuke za liječenje nisu standardizirane i jedinstvene.

Ključne riječi: **limfom, maskirani sindrom, intraokularno, ekstranodalno, intravitrealno liječenje, lokalna kemotrapija**