Chapter

Primary Intraocular Lymphoma: The Masquerade Syndrome

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Abstract

This chapter aims to provide a complete knowledge over the primary intraocular lymphoma (PIOL) and a correct clinical approach towards this rare condition, to avoid delays in diagnosis, which is considered the most important prognostic factor. A PIOL arises with no specific symptoms and could mimic both inflammatory and non-inflammatory ocular conditions. Also known as reticulum cell sarcoma in the past, PIOL is an ocular malignant condition, with a strong bond with primary central system lymphoma (PCNSL). This linkage is underlined by the fact that approximately 30% of the patients with PIOL have also PCNSL at presentation, while 45–90% will develop PCSNL in the following months. A correct diagnosis is currently achieved by the means of many different techniques: cytology, flow cytometry, immunohistochemistry, molecular analysis, and cytokines assay. Treatment of this condition has been completely revolutionized with the introduction of monoclonal antibodies directed against specific proteins present on the surface of lymphomatous cells.

Keywords: primary intraocular lymphoma (PIOL), primary vitreoretinal lymphoma (PVRL), masquerade syndrome, monoclonal antibodies

1. Introduction

An intraocular lymphoma is a heterogeneous group of malignant lymphoid neoplasia, which are divided into two main categories: those arising from vitreoretinal tissue (PVRL) and those deriving from uveal tract [1]. Lymphomas of the retina and/or vitreous are considered as a primary lesion, often with a concomitant central nervous system (CNS) involvement. Conversely, uveal lymphomas can be both primary diseases or metastasis of systemic non-Hodgkin lymphoma (NHL) [1, 2].

The most common form of PIOL is the vitreoretinal lymphoma, an extra nodal, non-Hodgkin, diffuse, large, B-cell lymphoma. Rare cases of primary T-cell vitreoretinal lymphoma can occur, but they are usually secondary to human T-cell lymphotropic virus type 1 infection or metastatic T-cell lymphoma [3–5]. Among immunocompetent individuals, the average incidence of vitreoretinal lymphoma is between 50 and 60 years, while in immunocompromised populations this condition develops earlier [6–8].

The most frequent pattern of presentation of PVRL is the infiltration of the sub-retinal pigment epithelium (RPE) in the form of lymphomatous aggregates and the presence of single neoplastic cells in the vitreous cavity [9, 10]. Although

less frequently than posterior segment involvement, some important findings in the anterior segment are: keratic precipitates, aqueous cells, flare, and iris nodules; however, these important elements are not specific for a correct diagnosis of intraocular lymphoma [8, 11].

Regarding the involvement of the central nervous system (CNS), the periventricular site is the most common way of presentation and would explain the tendency to spread to cerebrospinal fluid and leptomeninges.

The linkage between PVRL and PCNSL is variable, indeed CNS disease could occur before, following, or simultaneously with the ocular presentation; several previous studies show that 25% of patients with PCNSL will have the concomitant ocular disease at the time of diagnosis [12]. On the other hand 56–85% of individuals with PVRL will develop CNS involvement subsequently [13–16].

Therefore, PVRL is usually fatal. Despite its rare occurrence, PVRL remains a diagnostic and therapeutic challenge and the lack of effective therapeutic tools and delay in diagnosis may lead to a poor prognosis [17].

Previously misnamed as "reactive lymphoid hyperplasia" or "uveal pseudotumor", primary uveal lymphoma is a less common entity involving any region of the uveal tract, with a less-aggressive clinical course [18, 19]. Cockerham and associates re-evaluated pathological specimens of benign choroidal reactive lymphoid hyperplasia archived at the Armed Forces Institute of Pathology, and found out that 80% of these are low-grade, B-cell lymphomas [20] and that their subtype is of an extra-nodal, marginal zone or mucosa-associated, lymphoid tissue lymphoma [18]. Primary uveal lymphomas are typically quiescent, paucisymptomatic but with a marked propensity towards extraocular extension [18, 21].

Rarely they tend to turn into more malignant and aggressive tumors and, when treatment is necessary, they are very radiosensitive and carry a good prognosis [19, 20].

Despite the importance of the uveal form as well, we will exhaustively focus on the type of large B-cell intraocular lymphoma [1].

2. Epidemiology

Vitreoretinal lymphomas are rare tumors, with an annual incidence of 0.46 per 100,000 people, representing 4–6% of primary brain tumors and 1–2% of extra nodal lymphomas [12, 16, 22].

In the last 15 years, the incidence of this condition has tripled both in the US and in Europe. At the beginning, this increase in incidence was associated with the arise of immunocompromised persons due to AIDS condition, but since the introduction of highly active antiretroviral therapy, the development of intraocular lymphoma does not follow the decrease of patients with the acquired immune deficiency syndrome (AIDS) [23–26]. Iatrogenic immunosuppression may also lead to PIOL [27]. The cause for the increased incidence in immunocompetent patients is unknown [24].

3. Aetiology

The aetiology of PIOL/PCNSL is not very clear. Two theories have been implicated in PVRL development: infectious origin and hematological spread.

3.1 Infectious origin

According to the infectious theory, neoplastic transformation occurs into two steps: in the first one, viruses such as HIV or EBV, especially in

immunocompromised people, attack the lymphoid cells while, in the second one, it happens neoplastic transformation, that occurs in the CNS and/or in the eye.

This theory is supported by the frequent isolation of the EBV virus in AIDS patients with intraocular lymphoma, which also shows more aggressive characteristics [28]. In rare cases the parasite *Toxoplasma gondii* has also been isolated in patients with B-cell lymphoma, although the connection is much less strong than that with EBV and HIV [29].

3.2 Haematological spread

In hematological spread, neoplastic cells from nodal and extra-nodal sites spread to ocular and CNS structures [30]. According to this theory, B-cell chemokines may selectively attract lymphoma cells from the choroidal circulation to the retinal pigment epithelium (RPE) and/or retina. This theory is supported by the fact that B-cell chemokine receptors CXCR4 and CXCR5 were detected in the lymphoma cells, whereas the ligands BLC and SDF-1 were detected only in the RPE [31]. On this basis, it has been suggested that inhibition of B-cell chemo-attractants could be a future strategy for the treatment of PIOL [31].

4. Clinical presentation

4.1 Ocular features

Because its presentation can mimic a wide variety of ocular diseases, PVRL has often been addressed as a masquerade syndrome. Signs vary significantly between patients and are usually bilateral (64–83%) but often asymmetrical at presentation [1, 2]. Symptoms of hazy vision and/or floaters are the most commonly reported by patients.

4.1.1 Anterior segment

Anterior segment findings are usually uncommon and specific, including few anterior chamber cells, keratic precipitates [32, 33], presence of pseudo-hypopyon [34, 35], and iris and trabecular meshwork [27, 36], which could cause, respectively, heterochromia and secondary angle closure.

4.1.2 Posterior segment

Posterior segment examination reveals vitritis, ranging from mild to severe.

Lymphomatous cells present in the vitreous cavity are homogeneous and tend to be larger than the reactive cells of the immune system and they rarely aggregate each other in clusters. Ophthalmoscopically it's possible to observe clumps, strands, sheets and membranes that cause mild-to-severe vitreous haze; these rows of cells along vitreous fibrils give it a similar appearance to the "aurora borealis". Involvement of the retinal layer and/or RPE is manifested by creamy lesions with a characteristic yellowish appearance on examination of the fundus of the eye [14]. This can result in a characteristic "leopard skin" pigmentation overlying the mass [10]. Other retinal findings include: isolated subretinal lesions [37], exudative retinal detachment [37], RPE atrophy with subretinal fibrosis, and disciform scarring at the macula. Optic nerve infiltration may also occur [38]. Cystoid macular oedema is usually absent.

4.2 Central nervous system features

At presentation, 16–34% of PVRL cases have neurological involvement and it has been estimated that between 42% and 92% of patients can develop intracranial lymphoma within a mean interval of 30 months [14].

Neurological symptoms may occur at any time during the disease course and can be focal and/or diffuse. Most common symptoms include behavioral changes, alteration in cognitive function, focal neurological deficits (like hemiparesis or ataxia) and new-onset seizures (which is a strong indicator of neurological involvement).

Infiltration of the meninges by malignant lymphoma cells without intracerebral involvement can also be noted [12].

5. Diagnosis

5.1 Diagnostic approach

When a PIOL is suspected, it's necessary to exclude other types of uveitis. Therefore, the patient's examination should include chest radiography, complete blood cell count, erythrocyte sedimentation rate, routine blood chemistries, and other laboratory studies.

The definitive diagnosis of PIOL is based on the identification of atypical lymphoid cells in the eye, usually sampling the vitreous. However, it's possible to reach a diagnosis by demonstrating the presence of lymphomatous cells in the cerebrospinal fluid (CSF), avoiding the vitreous biopsy, because PIOL is a subtype of PCNSL.

Furthermore, because PIOL is closely related to PCNSL, neuroimaging of the brain and orbits and a lumbar puncture are required, to exclude a neurological involvement [39–41].

5.2 Ocular examination

5.2.1 Optical coherence tomography (OCT)

OCT facilitates the detection of many retinal abnormalities whose presence is related to PVRL [42].

The most common alteration on OCT is the evidence of hyperreflective signals (nodules, bands, and nods) at the level of RPE, corresponding to homogenous semi-opaque greyish spots in fundus photography. Those findings are instrumental proof of invasion and proliferation of the lymphomatous cells inside the retinal tissue. Anyway, it's important to differentiate these hyper-reflective spots from those which can be detected in other clinical entities (e.g., diabetic retinopathy, age-related macular degeneration, etc.) [43–45].

Apart from this, a wide range of other OCT findings associated with PVRL has been reported, including hyper-reflective subretinal infiltration, hyper-reflective infiltrates in inner retinal layers, RPE undulation, clumps of vitreous cells, and sub-RPE deposits [46]. Conversely, cystoid macular oedema is a rare finding [47].

5.2.2 Fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA)

The positive and negative predictive value of the combined use of FFA and ICGA is 89% and 85%, respectively [48].

The most common alteration on FFA is the presence of hypo-fluorescent spots, presenting with the so-called "leopard-spot" appearance [49].

Apart from this, a wide range of other FFA findings associated with PVRL has been reported, including punctate hyper-fluorescent window defects (55%), round hypo-fluorescent lesions (34%), and vasculitis (14%) were reported. Cystoid macular oedema did not exceed 2%. In addition, fluorescein leakage along retinal vessels and peri-arteriolar staining may also be seen in eyes with PVRL [43].

The most common alteration on ICGA is the presence of small hypo-fluorescent lesions in the early stages of PVRL, that become less obvious in later stages of the disease [49].

5.2.3 Fundus autofluorescence (FAF)

FAF may facilitate the detection of the active status of PVRL.

The most common alteration on FAF is the presence of a granular pattern of hyper-auto-fluorescent spots encircled by a hypo-auto-fluorescent ring [46]. Granular patterns were detected in several retinal areas, but this finding was not restricted to visible tumor location. Usually, these hyper-auto-fluorescents spots on FAF corresponds to the hypo-fluorescence spots on FFA (36%) and the hyperreflective spots on OCT (43%) [43].

It is noteworthy, that, after intravitreal administration of methotrexate, these hyper-auto-fluorescents spots become hypo-auto-fluorescent [42, 43].

5.2.4 B-scan ultrasound

There are no specific features for PVRL in ultrasound B-scan. However, B-scan can be very useful when visualization of the posterior segment is difficult.

Findings include elevated chorioretinal lesions, retinal detachment, vitreous debris, and enlargement of the optic nerve shadow [49].

5.3 Neurological examination

5.3.1 Imaging

Intraocular lymphoma with CNS involvement is evidenced by computed tomography (CT) and magnetic resonance (MR).

On CT it appears as an isodense or hyperdense lesion while on MR it provides a hypodense signal in both TI and T2 sequences [50]. If the diagnosis is swift, it is probable to find a single lesion up to 70% of cases; with the delay of diagnosis grows the possibility of finding multiple lesions. The most affected regions are: basal ganglia, corpus callosum, or periventricular subependymal regions [51].

5.3.2 Invasive procedure

A lumbar puncture should be performed to obtain cerebrospinal fluid (CSF), and this should be sent for routine cytologic, chemical, and cytokine analysis. Lymphomatous cells can be identified in the CSF of up to 25% of patients with known lesions on MR [50].

If lymphoma cells are found in the CSF, then a diagnosis of PCNSL can be made and no further diagnostic procedures are necessary.

In the cases with suspected CNS lesions on neuroradiological images and with negative CSF cytology, patients should undergo a stereotaxic biopsy of the brain lesion to reach a certain diagnosis [52].

In cases of both negative neuroradiological images and CSF cytology, it is necessary to acquire histological material through diagnostic vitrectomy of the eye most affected by the neoplastic process or in the one with the least visual acuity [33].

5.4 Ophthalmic biopsy

5.4.1 Bioptic material sampling

5.4.1.1 Vitreous biopsy

Vitreous represent the preferred tissue to sample in case of chronic uveitis of unknown cause or when an intraocular malignancy/infection is suspected. Furthermore, vitrectomy can also be performed in case of suspected PCNSL, when lumbar puncture and cytologic analysis of CSF fail to reveal neoplastic cells [53]. A final diagnosis of PIOL allows clinicians to start the appropriate treatment [54, 55].

Cytologic examination of vitreous biopsy has been employed to make a diagnosis of PIOL since the mid-1970s. The technique for performing a complete pars plana vitrectomy in a suspected case of PIOL follows typical protocol:

- a standard three-port pars plana vitrectomy is performed
- a complete core vitrectomy is recommended because the cytological analysis is standard [56] and molecular analysis with polymerase chain reaction amplification (PCR) and cytokine-level analysis are commonly performed [41, 57]
- the first vitreous sample is used for cytological analysis
- the second vitreous sample is diluted to allow a subsequent analysis of cytokine levels
- the vitreous fluid is also studied for microbiological aspects
- aware of the easy tendency of tumor cells to deteriorate, the sample of vitreous fluid is mixed with Roswell Park Memorial Institute (RPMI) culture medium to allow better maintenance and a more complete analysis of cells.

These sample must be analyzed by expert pathologists in the shortest possible time to increase diagnostic possibilities because of the rapid deterioration of cancer cells [58]. It must be stressed out that timing is essential because lymphomatous cells rapidly begin to degenerate.

Vitreous samples may not always contain neoplastic cells and, thus, be negative for the diagnosis of PIOL. This might happen when there is minimal vitreal involvement or when cells have degenerated. In such events, it may be necessary to perform another vitrectomy and send it to a well-qualified cytological laboratory [15].

5.4.1.2 External chorioretinal biopsy

Failure to identify malignant cells in the vitreous can occur and may be due to degeneration of the cells in samples, paucity of cells into the vitreous cavity, or lack of vitreal involvement. Indeed, lymphomatous cells may be confined solely to the sub-RPE and, in this case, an external chorioretinal biopsy (pioneered by Peyman and colleagues) may lead to a definitive diagnosis of PIOL [59–62].

The technique for performing an external chorioretinal biopsy in a suspected case of PIOL follows typical protocol:

- first, if the fundus is visible, laser photocoagulation is applied 1–3 days before surgery in a zone of the area to be biopsied. When vitreous is too hazy, endo-laser is performed immediately after pars-plana-vitrectomy
- a three-port pars plana vitrectomy is performed (in addition to an endo-laser if it was not performed before the surgery)
- a nearly full-thickness scleral flap is made, leaving one side attached to act as a hinge; when the flap of the sclera is retracted, the surgeon can visualize the choroids
- penetrating diathermy is located across the chorioretinal layer along the inner choroidal side
- appropriate chorioretinal tissue is provided by two opening incisions parallel to the limbus
- then one blade of a 0.12 nipper is inserted for the entire chorioretinal thickness
- finally, to allow the correct removal of a block of chorioretinal tissue, two further incisions, perpendicular to the limbus, are made with Vannas scissors
- finally, the scleral flap is locked.

5.4.1.3 Internal chorioretinal biopsy

Internal chorioretinal (transvitreal retinochoroidal) biopsy is another approach by which chorioretinal tissue is acquired [63].

Biopsy should be carried out as follow:

- a standard three-port vitrectomy is performed (sending undiluted and diluted vitrectomy to the pathology laboratory for analysis)
- endo-diathermy is used to outline an area of the retina that is of interest
- the intraocular scissors are taken to the vitreous chamber where they dissect the marked area of the retina
- then the intraocular scissors carry retinal tissue out of the eye through the entry site.

5.4.2 Bioptic tissue examinations

5.4.2.1 Histochemical staining

The cytological study of lymphomatous cells represents a standardized technique that has greatly been improved by different types of histochemical staining, such as Giemsa, E-E (haematoxylin-eosin) or Diff-Quick [1].

The main cytological features are: big atypical lymphoid cells with considerable, irregular nuclei and one to several prominent nucleoli, basophilic cytoplasm, rare

mitoses, and increased nuclear/cytoplasmic ratio [64]. The identification of lymphomatous cells is further complicated, in addition to their fragility, by the frequent reactive inflammatory infiltrate that accompanies the tumor response.

5.4.2.2 Immunophenotyping

Initial workup should always include immunophenotyping for B-cell markers (CD20, CD79a, PAX5) and T-cell markers (CD2, CD3), because atypical cells found in histochemical staining may also exist in certain reactive conditions, such as acute viral infection, leading to a misdiagnosis [65, 66].

Furthermore, immunophenotyping can detect the presence of monoclonality, which supports the diagnosis of lymphoma, because most PIOL are monoclonal B cell lymphomas that stain positively for B cell markers and show restricted expression of either kappa or lambda chain: indeed, a ratio of kappa/lambda light chains of >3 or <0.6 is considered as a reliable and useful marker for clonality expression [67].

Although most intraocular lymphomas arise from the B cell line, precursors from the T line can rarely be found.

This makes diagnosis much more difficult due to the lack of specific immunocytochemical markers.

Morphologically they can simulate a reactive inflammatory infiltrate but the immunohistochemistry for CD3 marker and the PCR for genetic rearrangements of TCR gene allow to discriminate these two different cell populations [68, 69].

In conclusion, cytology remains the diagnostic gold standard without forgetting, however, that flow cytometry guarantees important information for diagnostic purposes, indeed it can analyze several different markers simultaneously and has been used to confirm monoclonality in both B cell and T cell PIOL [1].

5.4.2.3 Cytokine's analysis

Although it's not diagnostic, analysis of the level of specific cytokines could give valuable information in the diagnosis of PIOL. Furthermore, it can be performed on the supernatant of the vitreous sample, sparing the main specimen for other exams.

The most useful cytokine is IL-10, which is an immune-suppressive cytokine, usually secreted by type-B lymphocytes, whose levels are elevated in both vitreous and aqueous humor (AH). Several studies have shown that interloquine 10 levels of at least 50 pg/mL in aqueous humor and 400 pg/mL in vitreous humor are strongly suspected for intraocular lymphoma.

Moreover, interloquine 10 levels into the vitreous became particularly valuable if compared to IL-6 levels (which is a pro-inflammatory cytokine commonly secreted by macrophages and T-cells): in fact, in other forms of uveitis (given the inflammatory nature of the process) IL-6 levels are lot higher than IL-10 ones, while in PIOL (due to the monoclonal proliferation of type-B lymphocytes) IL-10 levels became prominent. Therefore, also the relationship between the interloquine 10 and the interloquine 6 represents an effective method in placing the diagnostic suspicion of intraocular lymphoma; a ratio greater than 1 is very suggestive for tumor pathology.

On the other side, low interloquine 10 levels may be particularly helpful when a T-cell lymphoma is suspected [70].

5.4.2.4 PCR analysis

Molecular investigations of vitreous samples with PCR can be very useful in the research of lymphocytes' clonality, which is essential for the validation of PIOL diagnosis [70–76].

Detection of clonal immunoglobulin (IgH) and clonal T-cell receptor (TcR) genes rearrangements can contribute to the molecular diagnosis of B-cell and T-cell lymphoma, respectively [73–75].

However, obtain a significant result of genetic analysis, an adequate number of cells should be studied and this is not always possible due to the lack and fragility of lymphoma population [75, 77]. Moreover, with the aim of avoiding misinterpretation of minor clonal expansions as evidence of lymphoma, the results should be evaluated in the context of clinical and morphological features.

5.5 Differential diagnosis

PIOL is one of the most challenging masquerade syndromes. Due to its heterogeneous clinical features, diagnosis is often belated, inducing delayed therapeutic management with poor visual prognosis and life-threatening complications [14].

Differential diagnosis must consider the age of the patient and the clinical presentation. Further investigations will be mandatory to confirm the diagnosis, when possible.

5.5.1 Infectious entities

5.5.1.1 Viral retinitis

PIOL may masquerade as acute retinal necrosis (ARN), caused by a herpes virus infection, typically in immunocompetent patients. Necrosis usually starts at the peripheral retina, progresses rapidly towards the posterior pole, and is associated with vasculitis and dense vitritis. Retinal detachment may occur in 30–75% of cases during the disease.

PIOL may also masquerade as a CMV retinitis, that, conversely, typically occurs in immunocompromised patients.

In both cases, necrosis and hemorrhages can mimic a PIOL and differential diagnosis is confirmed only by AH or vitreous sampling and PCR analysis [78].

5.5.1.2 Severe ocular toxoplasmosis

The differential diagnosis with lesions caused by *Toxoplasma gondii* is very important; they are generally very characteristic already at the ophthalmoscopic examination in immunocompetent people but the greatest difficulties occur in immunocompromised patients because the involvement of anterior segment, vitreous cavity, and retinal scars can simulate the changes in RPE, typical of intraocular lymphoma.

It is therefore very important an appropriate analysis of the ocular fluid that allows isolating the parasite to differentiate the two conditions; nevertheless, in some cases of PIOL the parasite was isolated, suggesting a possible infectious origin of the lymphomatoid process [29].

5.5.1.3 Ocular lue

Syphilitic retinitis has very specific ophthalmoscopic and diagnostic characteristics that can allow to differentiate it from the forms of intraocular lymphoma.

It involves the peripheral retina and, more rarely, the posterior pole. It is associated with retinal vasculitis, moderate vitreous activity, and a modest spread to the anterior segment.

These lesions resolve without leaving any signs with appropriate antibiotic therapy and diagnosis is achieved thanks to serological examination.

5.5.1.4 Whipple illness

Whipple condition is a rare systemic disorder caused by *Tropheryma whipplei* which can present rare and late ocular manifestations such as uveitis and chorioretinitis with very disabling bleeding components [79]. Various neuro-ophthalmological manifestations have also been reported, such as ophthalmoplegia, supranuclear gaze palsy, nystagmus, myoclonus, ptosis, papilledema, or optic nerve atrophy.

Persistent vitritis along with retinitis may mimic PIOL. Specific antibiotics may cure the disease without corticosteroids.

5.5.2 Non-infectious entities

5.5.2.1 Granulomatous processes

The two conditions that mostly enter into differential diagnosis with intraocular lymphomas are sarcoidosis and TBC.

Both of these conditions affect older people and, specially, those with compromised immune defenses.

Although the presence of very specific elements such as posterior synechiae or cystoid macular edema enable an easy differential diagnosis with PIOL, in cases of the massive involvement of the posterior segment the clinical situation can be more difficult to define [80].

The further difficulty is given by the need to perform multiple tests to reach the correct diagnosis so that in some cases it is even necessary to analyze eye samples [81].

5.5.2.2 Bechet's disease

Bechet's disease occurs in young males more than females. Retinal necrosis is associated with dense vitritis, retinal vasculitis, and retinal vascular occlusion. Foci of retinitis may mimic areas of infiltration by PIOL and may resolve spontaneously.

Diagnosis is based on a set of criteria defined by the International Study Group for Bechet's disease.

5.5.2.3 Atypical Fuchs iridocyclitis

Fuchs iridocyclitis is typically unilateral disease that occurs in young adults and involves the anterior segment of the eye. Sometimes, it may also be associated with different types of intermediate uveitis as well as PIOL. Therefore, PIOL must be considered in atypical forms of FHC, especially when there is bilateral involvement.

5.5.2.4 Cryptogenic inflammatory processes

The presence of idiopathic inflammatory processes, especially in elderly and immunocompromised people, represents the most common and most difficult differential diagnosis.

These processes arise with completely nonspecific inflammatory affections, concerning the posterior segment.

In these cases, it's very important the diagnostic suspicion of lymphomatoid origin and clinicians should perform all the necessary analysis to discriminate this condition [82].

5.5.2.5 Miscellanea

Hodgkin's lymphomas can manifest themselves in the form of non-specific inflammatory processes of the posterior segment but, unlike PIOL, the vitreous involvement is much less evident [83].

Atypical uveo-meningitis that can mimic the clinical aspects of VKH syndrome and be resistant to common attack drugs should raise the suspicion of a lymphomatoid process [84].

Uveitis associated with the HTLV-1 virus provide ophthalmological characteristics very similar to PIOL; diagnostic investigations are therefore necessary for making a correct differential diagnosis [85].

6. Treatment

Optimal management for patients with PIOL requires a team of different specialists involving an ophthalmologist, The first line of treatment is high-dose systemic chemotherapy, associated with topical intravitreal chemotherapy and/or ocular radiotherapy, even in cases where no evidence of PCNSL is detected [2, 86].

6.1 Systemic chemotherapy

According to recent guidelines, systemic intravenous therapy with methotrexate represents the gold standard for the treatment of PIOL with a CNS and/or systemic involvement. Results show a very high remission rate, with an even better outcome when combined with other treatments [11, 87]. Several studies have also shown an increase in survival compared to treatments that did not include high doses of chemotherapy [88].

Among the many chemotherapic regimens including methotrexate, several studies reported that the MATRIX regimen (methotrexate, cytarabine, thiotepa, and rituximab) offers the best clinical outcome, with a higher success rate than methotrexate alone or any other form of a combination of drugs [89].

In cases with relapse or refractory response, treatment includes high dose chemotherapy with thiotepa, busulfan, and cyclophosphamide, followed by autologous peripheral blood stem cell transplantation [88].

6.2 Ocular chemotherapy

Ocular chemotherapy means the usage of specific chemotherapic agents administered intravitreally. Two local chemotherapic agents can be used in the treatment of PIOL: methotrexate and rituximab.

6.2.1 Intravitreal methotrexate

The use of intravitreal methotrexate, combined with systemic chemotherapy, has shown good results in the local control of PIOL. Currently, the dose is 400 μg in 0.1 mL and the plan assumes two injections per week during the first month, one injection per week in the next two months, and one injection per month during the following nine months, for a total of 1 year of therapy [90]. Same regimen is recommended in the treatment of relapsed PIOL [91–93], in the ocular relapse of PCNSL [94], and intrathecal chemotherapy [95].

Results show very high remission rates, while ocular complications are unlikely to happen and are essentially represented by transient changes in intraocular pressure and corneal epitheliopathy [96].

6.2.2 Intravitreal rituximab

The use of intravitreal Rituximab (an anti-CD20 monoclonal antibody) has recently been proposed for the treatment of CD20-positive PVRL [88]. The most studied treatment plan assumes one injection per week in four weeks.

Results show a high rate of the initial response to treatment, but there is still a high rate of tumor recurrence. In these cases, treatment can be with a new course of rituximab which has less toxicity than other chemotherapy drugs or by initiating therapy with methotrexate [97].

6.3 Radiation therapy

The use of radiation therapy for PIOL can vary according to various factors.

In forms of PIOL with exclusive ocular localization, local radiation exposure with external radiotherapy represents the current therapeutic standard, with an optimal dosage of 30–35 Gy administered in approximately 15 fractions [2, 98].

In cases, with concomitant involvement of both eyes and/or CNS and in cases in which systemic chemotherapy treatment has failed, panencephalic and ocular irradiation treatment can be added, but this could lead to complications both at the cerebral and ocular level, such as cognitive deterioration, ataxia, and, rarely, even death [98].

6.4 Rising treatments

In consideration of the continuous emerging of new resistance mechanisms put in place by cancerous cells against current therapies, there is a rising interest in developing new therapeutical approaches with engineered techniques.

One of the most studied strategies involves the use of FasL vesicles membranes, to stimulate the immune system to invade the eye (interrupting its situation as a privileged immune site) [99].

Another very promising strategy (tested only in animals) is the use of intraocular injection with recombinant immunotoxin HA22, which shows a very satisfactory response rate [100].

Other monoclonal antibodies (such as daclizumab, efalizumab, and alemtuzumab) have been tested and showed positive results in animal models [101].

Some authors described autologous stem cell transplantation as a possible therapeutic strategy in case of refractory and/or recurrent intraocular lymphomas, but, the lack of data does not allow to define of universal therapeutic standards as well as the correct chemotherapy regimen for transplant preparation [88, 102].

7. Prognosis

The diagnosis of PVRL is often delayed, due to late referral to an ophthalmologist: indeed, most patients present with unalarming symptoms, like persistent floaters but relatively preserved visual acuity.

The mortality rates between the various studies differ enormously.

This is partly due to the rarity of the disease which makes it impossible to identify a standardized and universally used therapeutic regimen, partly due to the clinical differences of the patients under examination.

Despite this, literature states that the rate fluctuates between 9 and 81%, guaranteeing an average survival of about 2 years from diagnosis [1, 98].

8. Conclusion

Management of PIOL is very challenging for the ophthalmologist because diagnosis is usually made difficult by the great capacity of this condition to masquerade other common ocular affections and treatment strategies that have poor clinical evidence (due to lack of cases). Anyway, in recent years the improvement of diagnostic techniques allowed a more rapid diagnosis and the development of new therapeutical strategies. The hope is that increasing in diagnostic efficiency and therapeutic perspectives could lead to the definition of univocal guidelines thanks to an increasing number of intraocular lymphomas to be subjected to various trials.

In conclusion, it's essential to create a multidisciplinary network of specialists involving an oncologist, onco-hematologist, and ophthalmologist to define the best diagnostic and therapeutic process.

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