Intraocular Lymphoma

David S. Bardenstein, MD

Intraocular lymphoma is the most elusive intraocular tumor to diagnose. Its clinical presentation can mimic benign conditions. Diagnosis is often based on obtaining an intraocular biopsy. Optimal management is not yet realized.

Methods: This report combines the experience of the author with a review of the current literature pertaining to intraocular lymphoma.

Results: Primary ocular lymphoma, a subtype of primary central nervous system (CNS) lymphoma, has a variable clinical course and frequently mimics benign inflammatory disease. Even when suspected, diagnosis can be elusive. Chemoradiation is the most effective treatment, but significant ocular and cerebral morbidity is associated with its use. Novel treatment regimens may reduce or eliminate side effects while preserving life, vision, and CNS function.

Conclusions: Primary CNS lymphoma with ocular involvement should be considered in patients with refractory uveitis, yellow-white choroidal masses, and CNS lymphoma. Aggressiveness in making the diagnosis should be tempered by the potential complications of the diagnostic process and advanced by the life-threatening nature of the disease. Treatment should attempt to maximize efficacy while incorporating considerations such as extent of disease and the patient’s age, health, and mental state.

Introduction

A variety of lymphoid proliferations can affect the eye. Intraocular structures can be involved in leukemia, non-Hodgkin’s primary central nervous system lymphoma (PCNSL), reactive lymphoid hyperplasia, and systemic non-Hodgkin’s lymphoma, typically of the small cell type. Intraocular lymphoma has been divided anatomically into vitreoretinal and uveal forms. The “vitreoretinal” form is associated with primary CNS lymphoma and is typically a large B-cell tumor (intermediate-grade lymphoma). In contrast, the “uveal” form is associated with systemic non-Hodgkin’s lymphoma and with involvement of orbital structures. It is typically small B-cell (low-grade lymphoma) proliferation and usually occurs with advanced systemic disease. Rare cases of T-cell lymphoma with ocular involvement have been reported. The apparent simplicity of this classification does not reflect the fact that the vitreoretinal form can involve the choroid and that the behavior of the vitreoretinal form appears to be altered in immunocompromised patients.

The literature on intraocular lymphoma is difficult to interpret. There are a few series of greater than 10 patients and numerous solitary case reports with literature reviews. A minority of series reflect patient management by a fixed group of physicians. The series data reflect idiosyncrasies of the institutions and time of evaluation (eg, patient source, availability of the wide range of modalities required for the diagnosis and management of this condition, and variability in the data regarding confirmation of histologic diagnosis and follow-up). The importance of isolated case findings has been inflated through re-citation of cases, and certain reviews have incorporated patients who have been multiply reported in the generation of epidemiologic data, which in some cases has led to significant distortions. This article attempts to sort through these issues. Epidemiologic information is provided as ranges rather than as specific numbers.

Nomenclature

The nomenclature of intraocular lymphoid proliferations can be confusing for a variety of reasons. The classification of lymphoma in general has been evolving as our understanding of lymphocyte pathobiology progresses. These classifications are not easily adaptable to the eye where no lymph node architecture exists.

Large-cell non-Hodgkin’s lymphoma involving the retina and vitreous with or without involvement of the CNS was referred to as reticulum-cell sarcoma or histiocytic lymphoma in the Rappaport classification. This terminology was based on the concept that large reticulum cells or histiocytes were pluripotential stem cells from which lymphocytes could differentiate. However, phenotypic analysis of cell type led to the concept that the small lymphocyte was the precursor cell from which large undifferentiated malignant lymphocytes arose. The large lymphocytes had been confused with histiocytes. The descriptive terms intraocular lymphoma and intraocular large-cell lymphoma were introduced to avoid further confusion over cell lineage. Studies using surface markers showed the majority of these expressed B-cell surface markers, while “null cell” types were next most frequent, and a minority expressed T-cell markers. Immunophenotypic analysis was first applied to a “primary intraocular lymphoma” by Kaplan et al, but this case was actually one of Richter’s syndrome.

New names continue to be introduced, including primary intraocular lymphoma, primary intraocular large-cell lymphoma (PILCL), and primary CNS lymphoma (PCNSL). The term oculocerebral lymphoma is adequate but neglects cases with spinal cord and cerebrospinal fluid involvement. Though no term will be completely accurate since the presentation is variable, the term primary CNS lymphoma with ocular involvement (PCNSLO) is probably the most acceptable since the ocular disease appears to be a subset of PCNSL, as the epidemiologic data below suggest.

Epidemiologic Characteristics

PCNSLO is rare, with fewer than 200 cases being reported. Most series include fewer than 25 patients. Since an indeterminate number of unreported and isolated cases have occurred, meaningful data regarding incidence and prevalence are not available. This type of lymphoma is estimated to represent 1% of non-
Hodgkin’s lymphomas, 1% of intracranial tumors, and far less than 1% of intraocular tumors. It typically affects elderly patients, with reported series having mean ages in the 60s. The youngest reported patient was 3 years old, and the initial case occurred in a 27-year-old patient. Women are affected up to twice as often as men, and there is no racial predilection. PCNSLO may be unilateral or bilateral on initial presentation, but ultimately, 80% to 90% of patients will have bilateral involvement. Intracranial disease occurs in 56% to 85% of patients with ocular disease, and recent estimates suggest that 15% to 25% of patients who present with CNS disease will have ocular disease, hence the distinction between PCNSL and PCNSLO. Data regarding the cause of PCNSLO are not conclusive at this time, although PCNSLO appears to occur with increased frequency in persons who are severely immunosuppressed (see below).

Symptoms and Presentations

In 50% to 65% of cases, PCNSLO presents in the eyes. The most common subjective symptoms are painless decreased vision and “floaters.” The typical clinical profile is an elderly patient with uveitis that is refractory to treatment. Other common presentations include photophobia, red eye, or patients with known PCNSL in which ocular disease is discovered on screening examination. Less common presentations include exudative retinal detachment, fundus mass, ocular pain, glaucoma, neovascularization, optic neuropathy, and a variety of chorioretinal abnormalities. Because of its insidious onset and ability to simulate other conditions, delay in diagnosis is common. However, increased awareness of this entity has led to a decrease in the mean interval from the development of symptoms to the time of diagnosis at one tertiary institution from 24.3 months in cases seen before 1980 to 5.8 months in cases seen after 1980. At a quaternary institution, the mean interval was 21.4 months in cases seen after 1980.

Ophthalmologic Findings

Anterior Segment

Vision loss is frequent in PCNSLO and may vary from mild to severe. With extensive disease, circulating tumor cells can appear in the anterior chamber in up to 75% of patients. The cells simulate iridocyclitis and can even form a pseudohypopyon. Secondary anterior segment changes include neovascularization of the iris and iridocorneal angle with possible glaucoma. In rare circumstances, PCNSLO can form a mass in the iris or angle.

Posterior Segment

Vitreous cells are a typical finding and are present in most cases (Figs 1A-B). It does not require many cells to produce a hazy view for the examiner, and the presence of cells can be suspected by the non-ophthalmologist when diffuse haziness obscures details of the optic nerve and retina during direct ophthalmoscopy. Differentiation of vitreous haze from other causes of limited view of the posterior pole of the eye requires evaluation by an ophthalmologist.

The characteristic fundus lesion is a low-lying, yellow-to-white mass deep to the sensory retina. Lesions may be single or multiple, confluent or discrete. They may even appear as multiple punctate lesions (Fig 2). Lesions may be infiltrative and involve all layers of the retina, thereby making it difficult to identify precisely which layers of the tissue are involved. The presence of subretinal pigment epithelial masses is felt by some to be pathognomonic of PCNSLO. Retinal hemorrhage is only rarely prominent, and a distinct tumor intrinsic vasculature, as seen in primary choroidal tumors, is typically absent from the lesions. The deep location of the infiltrates can give rise to a nonrhegmatogenous retinal detachment. If chorioretinal lesions regress, scarring and atrophy of the retinal pigment epithelium may be the only remaining fundus findings. On rare occasions, PCNSLO presents as a single solitary intraocular mass simulating an amelanotic melanoma.

Systemic Findings

Involvement of the CNS by tumor can result in alteration of cognitive function. The spread of PCNSL to other regions is infrequent. In autopsy studies, only 7% to 8% of cases show such spread. Most reports of systemic involvement by PCNSLO appear to represent diffuse large-cell lymphoma.

Clinical Differential Diagnosis
Clinical differential diagnosis includes reactive lymphoid hyperplasia (RLH), spread of systemic lymphoma, primary uveitis, infection, metastatic tumor, and anaplastic melanoma. All of these (except uveal melanoma) not uncommonly may have CNS involvement. Reactive lymphoid hyperplasia and spread of systemic lymphoma within the eye are the most difficult entities to distinguish from PCNSLO since they are histologically similar. Predominance of vitreoretinal involvement supports the diagnosis of PCNSLO, while primarily choroidal involvement and evidence of other non-Hodgkin’s lymphoma supports “metastatic” spread to the choroid. The age distribution of RLH is similar to that of PCNSLO but is more often unilateral. Tissues involved by RLH are thickened and may have overlying exudative fluid elevating the retina. Systemic or nodal involvement supports RLH or non-PCNSLO small- or large-cell lymphoma.

Primary uveitis can show diffuse choroidal infiltrates but may have a vasculitic component. Uveitis may also be associated with other systemic manifestations. Cytomegalovirus (CMV) retinopathy is an important consideration in the clinical differential diagnosis since it can present with whitish-yellow retinal diffuse lesions and cellular infiltrates in the vitreous and anterior chamber. CMV retinopathy is much more common than intraocular lymphoma and is even more likely in the current era with increased incidence of infectious immunosuppression and the increased use of powerful immunosuppressive agents in anticancer chemotherapy or in association with bone marrow transplantation. Proper diagnosis is critical since CMV retinopathy can be acutely and permanently blinding. Typical features that support the diagnosis of CMV retinopathy include hemorrhage and a perivascular distribution. A more subtle feature is the granular nature of the necrotic retina in CMV when compared with the exuberant creamy nature of the lymphomatous infiltrate. PCNSLO can cause arteriolar obstruction, resulting in retinal necrosis.

Metastatic carcinoma is the most common intraocular malignancy. Metastases typically present as yellow-white choroidal masses and frequently have mottled brown pigment in the overlying retinal pigment epithelium. Their boundaries can be diffuse but are often distinct. Retinal necrosis is not seen with metastases. A history of the primary cancer often can be obtained.

Ancillary Studies

Imaging

Evaluation of patients with intraocular lymphoma includes high-resolution neuroradiologic imaging of the CNS with contrast. Current consensus is that magnetic resonance imaging (MRI) is superior to computed tomography (CT) in detecting lymphoid lesions in the CNS. While either CT or MRI is a standard part of the systemic evaluation, neither is helpful in evaluation of ophthalmic disease. However, B-scan ultrasonography was abnormal in 7 of 7 patients studied, showing either vitreous debris or a thickened retina, choroid, or optic nerve.

Laboratory Studies

Lumbar puncture to obtain cerebrospinal fluid (CSF) for cytology is indicated if the patient is believed to have lymphoma. This procedure can be performed at the time of vitreous biopsy. Serologic studies are typically obtained to evaluate for entities in the differential diagnosis of PCNSLO. These can include rapid plasma reagin (RPR) screening, fluorescent treponemal antibody absorption (FTA-Ab) testing, toxoplasma titer, human immunodeficiency virus (HIV) testing, angiotensin converting enzyme, and cytomegalovirus titer. A tuberculosis skin test is also recommended. HIV testing is important because HIV-positive individuals are at increased risk for not only PCNSLO, but also other entities in the differential diagnosis of PCNSLO. Additionally, PCNSLO is believed by some to have different extent of intraocular involvement and clinical behavior in patients with acquired immunodeficiency virus (AIDS). Bone marrow aspiration that is used for staging systemic lymphomas is of limited value since only 8% of patients will show systemic spread, even at autopsy.

Diagnosis

The diagnosis of intraocular lymphoma requires histologic analysis. Because of its subtle symptoms and variable presentations, a high index of suspicion is an important component in making the diagnosis. The steps taken in making the diagnosis will depend on the presentation. For example, in a case with typical fundus lesions, one might proceed rapidly to biopsy, while in a case with vitritis or retinitis alone, laboratory evaluation to detect possible inflammatory or infectious conditions is usually undertaken before invasive techniques are employed.

A variety of methods can be used to obtain intraocular material for analysis. Due to progressive risk to the eye, these methods should be used in a stepwise fashion. Advances in intraocular surgery techniques have led to the development of methods for obtaining chorioretal biopsies that previously were associated with a high risk.

One key factor in obtaining accurate diagnosis is a cytopathologist with experience in diagnosing large-cell lymphoma and, preferably, experience with intraocular specimens. The presence of the cytopathologist in the operating room allows change to another diagnostic method in cases of nondiagnostic or inadequate material. Finally, even in the best of hands, multiple specimens may be required before an unequivocal diagnosis of PCNSLO can be made.

Vitreous biopsy remains the mainstay for diagnosis of PCNSLO. Vitreous samples are typically less cellular than the clinical appearance would suggest, and the diagnosis is often made based on a limited number of cells. In addition, nonepithelial lymphocytes may be present in the specimen so that the actual number of neoplastic lymphocytes is lower than expected. Another factor complicating the diagnostic process is tumor location. Subretinal tumors are not accessible by vitrectomy techniques unless a retinotomy is performed using a vitreous approach.

Vitreous aspiration biopsy is a safe technique whose advantage is the best preservation of cytomorphology. Material is aspirated directly through a 25-gauge needle into a syringe. In some cases in which diagnosis could not be made on material obtained through the mechanical vitrector due to artifacts, diagnosis was subsequently made with directly aspirated material.

The next level of biopsy technique utilizes the mechanical vitrector. This allows better management of tissue during the procedure and the ability to obtain more specimen. Specimens are often diluted and appear to undergo some artifactual change since malignant lymphocytes are fragile to the effects of mechanical disruption. Material may be lost in the tubing. In contrast to vitreous aspiration, vitreous biopsy also allows removal of sufficient material to improve vision in symptomatic cases.

If vitreous samples do not provide diagnostic tissue in the presence of retinal lesions, retinal and chorioretal biopsies or subretinal aspiration can be performed. Either an intraocular or a transscleral approach can be used. With advanced vitreoretinal techniques, the retinotomy required for sampling by the intraocular route can usually be safely managed, and the intraocular technique adheres to the principle of preserving anatomic boundaries to contain tumor. Subretinal aspiration combines the features of minimal tissue disruption with direct access to the tumor and has been useful when diagnostic material was not available from the vitreous. In extremely rare cases, when vision has been lost or the need for diagnosis is desperate, diagnostic enucleation can be performed.
In attempts to derive more diagnostic data from vitreous specimens that might be less affected by surgical artifact, cytokine levels in the vitreous were studied. Elevated levels of IL-10 were found in the vitreous of patients with PCNSLO but not in those with uveitis. When the ratio of IL-10:IL-6 levels was calculated, all patients with PCNSLO had ratios greater than 1, while in specimens from eyes with uveitis, the ratio was less than 1. Comparison in CSF showed a statistically significant difference but less sensitivity; specimens with lymphoma cells showed elevation in 50% and those without cells showed elevation in 13%.

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Neoplastic cells can also be found in the CSF in approximately half of cases, though like vitreous, it may require multiple attempts to obtain a diagnostic specimen.

Of interest are the data from a larger study in which only half of patients suspected of having intraocular lymphoma received that diagnosis following vitrectomy. While it is emphasized that PCNSLO frequently masquerades as uveitis, it is of great interest that one study in which 71 consecutive elderly patients presenting with uveitis after age 60 years contained no patients with intraocular lymphoma. However, this study did not separate unilateral as opposed to bilateral involvement.

**Histology**

**Vitreous Biopsy**

The typical histology of vitreoretinal aspirates in PCNSLO consists of sparse numbers of cells. Frequently, specimens contain mature inflammatory cells in addition to large neoplastic lymphocytes and necrotic debris. Thorough evaluation of the entire specimen may prevent under-diagnosis. Cells of large-cell lymphoma show nuclei with irregular contours and coarse chromatin and nucleoli (Fig 3). Nuclear membranes can fold to form “snouts.” Cytoplasm is scant. Because of the fragility of neoplastic lymphocytes, a specimen may contain numerous abnormal-appearing but uninterpretable cells.

**Histopathology**

In whole eyes examined after enucleation or at autopsy, tumor cells can involve the vitreous, retina, optic nerve, or choroid. They are found less often in the anterior segment. Clusters of cells may be seen in the neurosensory retina, in the subretinal space, and between the retinal pigment epithelium and Bruch’s membrane (the basement membrane separating the choroid and retina) (Figs 4 and 5). The choroid of immunocompetent patients often contains nonneoplastic inflammatory cells. When present, choroidal involvement by PCNSLO is typically diffuse, whereas retinal involvement may be more perivascular. When present, retinal necrosis can be extensive. Nonmalignant lymphocytes can be present either mixed with neoplastic lymphocytes or in separate aggregates. Conflicting observations have been made regarding the incidence and possible meaning of compartmentalization of neoplastic B cells and reactive T and B cells between the choroid and retina in PCNSLO. Some have claimed that in nonimmunocompromised patients, nonneoplastic T cells (but not neoplastic B cells) are localized to the choroid, while in immunocompromised patients, neoplastic B cells are found in both the choroid and retina. These observations require further confirmation.
Immunophenotypic Analyses

Immunophenotypic analysis has been an important and constantly evolving modality in understanding PCNSLO. The data from some early studies are difficult to compare to current data. With current immunohistochemical analysis of lymphocyte markers, almost all intraocular lymphomas are composed of B cells. Certain early series identified significant numbers of tumors showing no immunophenotypic label as null-cell tumors, but this was probably related to the quality of the antibodies used. Other cases reported and re-cited by others as intraocular T-cell lymphoma were in fact not primary ocular lymphomas. Current review of cases presented in the literature with appropriate technique and documentation suggests that over 90% of PCNLs express B-cell markers. The remaining cases can represent false-negative B-cell, T-cell, and null-cell tumors. Two primary angiocentric T-cell cases have been described that had a distinct presentation mimicking retinal vasculitis. The further resolution of this question will depend on wider application and better understanding of molecular genetics techniques.

Treatment

Treatment of PCNSLO remains controversial since treatment series are small due to the rarity of the condition. Treatment modalities are rapidly evolving. The issues that must be considered and balanced include the efficacy of treatment in reversing the disease process against the overall poor prognosis of the disease, the extent of disease, and the morbidity to the eye (e.g., blood-aqueous barrier breakdown, cataract, dry eye, corneal abnormality, radiation retinopathy, and optic neuropathy) and to the CNS (dementia) of the chemoradiation protocol.

Treatment should be initiated when staging is complete since the lens, cornea, retina, lacrimal gland, and perhaps the optic nerve are all radiosensitive at relatively low levels, and the need to reirradiate with overlapping fields could hasten and worsen complications.

Treatment of intraocular lymphoma underwent a significant advance with the introduction of chemoradiation to the CNS and ocular radiation. Radiation (35 Gy to 40 Gy) alone to the eyes and CNS gave high rates of initial response, but patients usually succumbed to recurrent disease. With multimodality therapy including a boosted radiation dose (5 Gy to 10 Gy) to the spinal cord and intrathecal methotrexate, vision can be improved and life can be prolonged, with some patients alive at 9 years posttreatment. In selected cases, some individuals treat patients with isolated ocular disease with ocular radiation alone with some longer-term survivors.

Recent innovations in treatment include multi-agent primary chemotherapy. This approach was designed to reduce radiation-associated cognitive defects that can occur in up to 40% of patients above 50 years of age. The regimen included methotrexate and procarbazine and some patients also received vincristine, thiopeta, or both vincristine and cytarabine. Some patients required radiation or further chemotherapy for relapse, but complete remission was seen for as long as 30 months. Most importantly, with the prolonged survival in this study, radiation-induced cognitive loss occurred in only one patient and improved in eight of nine patients.

Others have augmented standard primary treatment by chemoradiation with systemic methotrexate and cytarabine, observing 3 of 3 cases with 24-month complete remission. Cytarabine and methotrexate have been used in combination for salvage. Intravitreal methotrexate has been used to reduce the extent of intraocular tumor in patients who have undergone chemotherapy with or without radiation with good success at preserving vision.

Other techniques that may be useful include the pharmacologic breakdown of the blood-brain barrier with intra-arterial mannitol to increase the levels of chemotherapeutic agent. Others have treated a small number of refractory patients with chemotherapy and total body irradiation followed by bone marrow transplant with unclear results. Further study of these modalities is needed.

The use of anti-inflammatory and immunosuppressive agents prior to establishment of the diagnosis may complicate management of PCNSLO by suppression of the disease with subsequent delay in diagnosis. In addition, corticosteroids are believed to increase the fragility of the tumor cells, thereby making cytologic and histologic diagnosis more difficult.

Serial Evaluation

Our recommendation is for serial examination every three months and neuroimaging studies and systemic evaluation every six months. The recommended interval for re-evaluation after treatment response has occurred should be guided by patient status and can reflect examiner preference.

Prognosis

Even with chemoradiation, prognosis remains poor for patients with PCNSLO, and many succumb to CNS disease within two years. Yet, median survival of PCNSL has increased from 1-1.5 to over 3 years with newer therapies. However, features affecting prognosis of PCNSLO are not well understood since treated patients may survive for up to a decade, even with treatments such as enucleation and isolated ocular irradiation. PCNSLO data are more limited but appear to show the same trend. It is hoped that the trend toward longer survival will continue with the introduction of new therapeutic regimens.

Other Intraocular Lymphoid Proliferations
Leukemia

Leukemic involvement of the eyes is probably the most common form of ocular lymphomatous proliferation. There is a discrepancy between the frequency of involvement reported clinically and at autopsy.\(^\text{30-41}\) Histopathologically, involvement of the eye was seen in at least 65% of cases. Clinically, in a prospective study, tumor-related leukemic fundus findings were seen in only 3% of cases, though non-tumor-related clinical abnormalities were seen in 40% of patients, almost all of which were related to abnormal hematologic conditions and vascular pathologv.

Immunosuppression, Viral Infection, and PCNSLO

Large B-cell lymphomas develop with increased frequency in patients with systemic immunosuppression that occurs with transplantation, HIV infection, and certain viral infections. PCNSLO has been described in these settings, either alone or in combination with orbital tumor.\(^\text{42-45}\) Anecdotal evidence suggests that PCNSLO is more aggressive in immunosuppressed patients and that this is associated with the absence of nonneoplastic reactive T cells in the choroid, thus allowing greater spread of lymphoma cells to the choroid. Intraocular lymphoma resembling PCNSLO has been seen in patients infected with human T-cell lymphotropic virus-1 (HTLV-1) and Epstein-Barr virus.\(^\text{46,47}\)

Special Cases of PCNSLO

The occurrence of diffuse large-cell lymphoma after chronic lymphocytic leukemia is known as Richter’s syndrome. While ocular involvement has been seen in such cases, these are diffuse lymphomas and thus not comparable to PCNSLO.\(^\text{3,49}\)

References


*From the Department of Ophthalmology, University Hospitals of Cleveland, Ohio.*

Address reprint requests to David S. Bardenstein, M.D., Assistant Professor of Ophthalmology, 639 Wean Building, Department of Ophthalmology, Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Cleveland, OH 44106.