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Ocular manifestations and treatment of central nervous system lymphomas

KAAN GÜNDÜZ, M.D., JOSE S. PULIDO, M.D., M.P.H., M.B.A., COLIN A. MCCANNEL, M.D., AND BRIAN PATRICK O'NEILL, M.D.

Retina and Vitreous Surgery Service, Department of Ophthalmology; and Department of Neurology, Mayo Clinic, Rochester, Minnesota

✓Intraocular primary central nervous system lymphoma (PCNSL), also called primary intraocular lymphoma (PIOL), is a subset of PCNSL in which lymphoma cells invade the subretinal pigment epithelial space and vitreous cavity with or without central nervous system involvement at the time of ocular diagnosis. The frequency of this rare condition has increased over the past years in immunosuppressed as well as immunocompetent patients. The authors review the current status of PIOL and elaborate on their group's experience with its diagnosis and treatment.

The incidence of PIOL is increasing. There is evidence that chronic antigenic stimulation may result in the development of PIOL. Recent advancements in the diagnosis of PIOL include better handling of vitreous specimens for cytological studies, immunocytological investigation for lymphoid cells, flow cytometry, cytokine evaluation, and molecular analysis. Because PIOL has a nonspecific presentation, the differential diagnosis should include infectious and noninfectious causes presenting with vitreitis and/or subepithelial infiltration as well as paraneoplastic syndromes including CRMP-5 optic neuropathies. Given that therapy is long-term and has significant systemic and ocular complications, tissue diagnosis is important. Treatment of PIOL may include systemic chemotherapy in which high-dose methotrexate-based regimens are used as well as intraocular injections of methotrexate and rituximab (anti-CD20 antibody). Cranial and ocular external-beam radiotherapy is being used less often today.

Further studies are needed to prevent the tumor formation in terms of eliminating antigenic load and inhibiting B-cell chemokines as well as to determine the optimal local and systemic chemotherapy and immunotherapy options in the management of PIOL.

KEY WORDS • primary central nervous system lymphoma • primary intraocular lymphoma • optic neuropathy • radiotherapy • chemotherapy • methotrexate • cytarabine • rituximab

THE information about intraocular lymphomas has been somewhat clouded because of the incorrect grouping of distinct entities under the same rubric.[14,57] There are three distinct forms of intraocular lymphoma. One originates within the CNS and is called intraocular PCNSL or PIOL. This entity can occur with accompanying or prior involvement of the brain (secondary) or with eye involvement only (primary). The PIOL is the form that will be discussed primarily in this review (Table 1). The second type arises outside the CNS and involves the eye.[27] This form can involve the retina–vitreous compartment of the eye or the choroid. This form should be called "secondary intraocular lymphoma with vitreous and retinal involvement" or "secondary intraocular lymphoma with choroidal involvement." The third type involves the choroid alone and may have no evidence of systemic involvement.[25] This form should be called "primary choroidal lymphoma."

Although PIOL is a rare disease, its incidence has dramatically increased in the past 20 years. This entity accounts for approximately 1% of all uveitis cases encountered in ophthalmic practice settings.[32] The PIOL involves primarily the vitreous cavity and specific sites in the retina, including the subretinal space or the subretinal pigment epithelial space, but not the choroid.[43] These areas are immunologically privileged and separated from the systemic circulation by the blood–retinal barriers and the Bruch membrane of the choroid. In contrast to PIOL, the metastatic systemic lymphoma is usually confined to the uvea, particularly the choroid, although there are cases that involve the retina and vitreous cavity.[47]

In general, PCNSL accounts for 4 to 7% of brain tumors,[12,30,40] and this lesion occurs with a markedly increased incidence in the immunosuppressed population. It is seen in posttransplant patients, in those who are infected with human immunodeficiency virus, and in patients with congenital or iatrogenic immunosuppression.[10] Paradoxically, in patients in whom immunocompetence can be restored by cessation or reduction of antirejection medication and use of highly active antiretroviral treatment, the overall outcome may be better than in those without obvious immunosuppression. The incidence of this disease has increased in the past two decades in immunocompetent

Abbreviations used in this paper: CNS = central nervous system; IL = interleukin; MR = magnetic resonance; PCNSL = primary CNS lymphoma; PIOL = primary intraocular lymphoma; WBRT = whole-brain radiation therapy.

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TABLE 1

Proposed nomenclature for ocular lymphomas

extraocular lymphoma
primary
conjunctival
orbital
lacrimal
secondary
conjunctival
orbital
lacrimal
intraocular lymphoma
primary
choroidal
PIOL
secondary
choroidal
PCNSL
vitreoretinal intraocular lymphoma

patients as well. This increase in incidence can be attributed to the better diagnostic imaging and biopsy sampling methods that became available in recent years.[16] However, other factors may be at play, including more widespread use of corticosteroid drugs and hormone replacement therapies.[45] In immunocompetent patients, the mean age of onset of PCNSL is approximately 60 years and there is a slight male preponderance, although this has not been verified in all series.[4,8,9]

Other Types of Ocular Lymphomas

Systemic lymphomas outside the CNS are rarely associated with retinal or vitreous involvement, but it does occur.[47] Systemic lymphomas usually involve the choroid. Choroidal involvement in these cases can be unilateral or bilateral. Separation by the Bruch membrane tends to prevent choroidal lymphomas from spreading into the subretinal space. Primary or secondary choroidal lymphomas tend to be low-grade B-cell non-Hodgkin lymphoma, and for the most part their prognosis is better than the one for PIOL.[26,47] Some cases that used to be called uveal lymphoid proliferation have subsequently been found to be primary choroidal lymphomas.[27]

Orbital and conjunctival lymphomas can be solitary or associated with systemic disease. Occasionally they can have choroidal involvement as well; however, most of the time they tend to be extraocular. Orbital lymphomas have a molded appearance conforming to the shape of the globe and orbital walls on imaging studies.[26] Extraocular lymphomas are generally low-grade lymphomas, and some cases may be associated with *Helicobacter pylori* or *Chlamydia psittaci* infections.[18]

Clinical Findings in PIOL

The age of onset of PIOL ranges from 15 to 85 years, with a mean age of late 50s to 60 years.[8,10,32,43] Both sexes are affected and most series point to a higher incidence in women, with a female/male ratio as high as 3:1 in some series.[8,10,41,43] This is unlike PCNSL, for which a modest male predominance is reported in most studies.

Typical clinical symptoms of PIOL include blurred vision and floaters. In many of these patients uveitis is initially diagnosed, especially if there is no known history of cerebral involvement. The most common manifestations are similar to those seen in patients with posterior uveitis or vitreitis, combined anterior and posterior uveitis, or subretinal pigment epithelial infiltrates.[7,10,39] The anterior segment findings of keratic precipitates, aqueous cells, and aqueous flare are suggestive of inflammation, although hypopyon is not seen in these cases, and anterior chamber involvement is usually rare or mild. The presence of clumps or sheets of cells in the vitreous cavity is a common finding (Fig. 1). Focal, multifocal, or diffuse chorioretinal infiltrates are also seen with or without vitreous cells. Multifocal subretinal pigment epithelial infiltrates leading to overlying retinal pigment epithelial detachments are considered to be pathognomonic (Fig. 2).[9] As opposed to patients with retinitis from inflammatory causes, these patients tend not to have retinal pigment epithelial and retinal scarring in areas next to active disease. The scarring would imply a creeping inflammatory process that spreads around the eye as opposed to an active infiltrative process, which would be more commonly seen with PIOL. In an infiltrative process there would be continued growth, and this would not leave scarring around the actively involved area. Sometimes, PIOL presents with optic neuropathy, vasculitis, retinal hemorrhages, and retinal detachment.[39,44]

Many patients initially receive topical and/or systemic corticosteroid agents for possible uveitis. Most forms of intraocular lymphoma tend to respond to steroid treatment, but the response is transient and the disease recurs.[39] Many of the patients have even received repeated doses of corticosteroid drugs when their visual symptoms reappeared after medications were tapered off. This steroid dependence or lack of response to steroid treatment may be the initial clue that the patient has some form of intraocular lymphoma.

In most series a median interval of 21 to 24 months from the onset of ocular symptoms to definitive diagnosis is reported.[14,57] Nevertheless, PIOL is being diagnosed earlier, and recent evidence leads us to suggest that the diag-

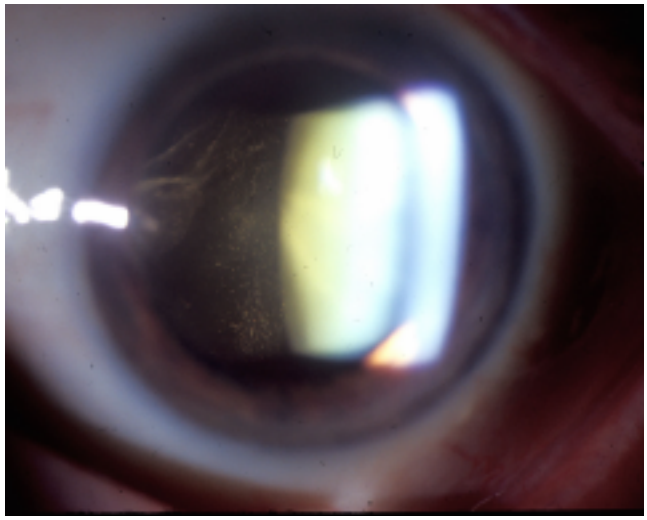


FIG. 1. Color photograph of white vitreous cellular infiltrates producing a hazy view of the fundus in a patient with PIOL.

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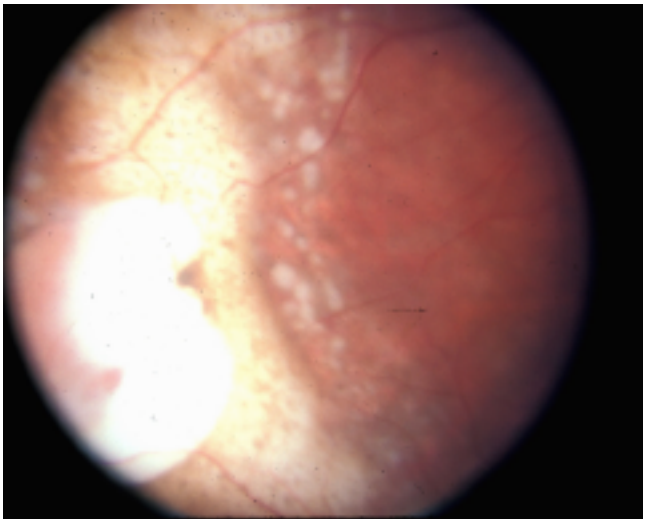


FIG. 2. Color fundus photograph of subretinal pigment epithelial infiltrates presenting as white, punched-out lesions in PIOL.

nosis can be achieved within 12 months in 80% of these patients.[3] Ocular involvement may precede, occur simultaneously, or follow the CNS disease. Primary CNS lymphoma develops in approximately 80 to 90% of the patients with PIOL.[31,42] The CNS progression can develop within months of the onset of visual symptoms from PIOL. Therefore, once the diagnosis of PIOL is established, neurological staging that includes MR imaging of the neuraxis and lumbar puncture should be performed to rule out CNS involvement. On the other hand, approximately 25% of patients with PCNSL demonstrate eventual intraocular involvement.[9]

Cranial MR imaging reveals multifocal disease in 30 to 40% of patients with PCNSL.[16] The tumor is hypo- to isointense on T_1-weighted MR images, hyperintense on T_2-weighted images, and demonstrates marked contrast enhancement.[12] The frontal lobe is the most commonly affected region of the brain; however, the corpus callosum and basal ganglia are also frequently involved. Primary CNS lymphoma has an affinity for the periventricular region of the brain. Leptomeningeal involvement can also occur, leading to cranial neuropathies.[12,16] Analysis of CSF reveals a positive cytological examination in approximately 10 to 20% of cases.[12] The most common symptoms in PCNSL are cognitive impairment and personality changes, followed by lateralizing signs such as hemiparesis, aphasia, and a visual field defect.[16] Seizures are present in 15 to 20% of patients. The eventual diagnosis of PCNSL, however, may require stereotactically guided biopsy sampling of the deep lesions seen on MR imaging.[16]

Patients with testicular lymphoma are at risk for relapse, particularly in the CNS.[54] Clinicians should suspect intraocular lymphoma in patients with a history of testicular lymphoma who present with vitreitis or retinal lesions.

Pathological Features

Ocular lymphomas were initially described as reticulum cell sarcoma or histiocytic lymphoma of the eye until it was recognized that the cells of origin were lymphoid and not histiocytic types.[10,14,48] A PIOL is usually a diffuse large B-cell lymphoma. This is in contrast to choroidal lymphoma, which is usually a small B-cell lymphoma, representing low-grade disease. The tumor cells are large pleomorphic lymphocytes with scant cytoplasm and hyperchromatic, hypersegmented nuclei with prominent multiple nucleoli.[10] Reactive lymphocytes, macrophages, necrotic debris, and fibrinous material are often seen and can obscure the correct diagnosis. In addition to tumor cells, the choroid may be infiltrated by active T cells in patients with PIOL, in contrast to systemic lymphoma with ocular involvement, in which the choroid is infiltrated by tumor cells alone.[10] More than 95% of PIOL cases are B-cell lymphomas that express pan–B-cell markers such as CD19 and CD20; rarely, the tumor can also be of T-cell lineage.[10,46]

Pathogenesis

The PCNSL and PIOL types represent rare forms of extranodal non-Hodgkin lymphoma that are confined to the CNS and the eye, respectively. The pathogenesis of PIOL is unknown, although one hypothesis is that this entity originates from lymphocytes activated and transferred by exposure to the pathogen or antigen in the globe; chronic antigen stimulation results in the development of a monoclonal lymphoproliferative response.[6,39,51] A second possibility is that transformation occurs outside the globe and that the malignant cells get trapped in the immunoprivileged structures of the eye (vitreous cavity, subretinal space, and anterior chamber), which promotes tumor growth while the systemic clone is eliminated by the intact immune system. This theory may explain the formation of a multicentric tumor, if the lesion is captured in immunoprivileged sites such as the globe, testes, and CNS. This may be a mechanism for B cells arising in other sites and developing particular patterns of adhesion molecules, permitting homing to the CNS, where such cells could proliferate and transform in the relative absence of immune regulation.

In immunosuppressed patients, PCNSL is nearly always associated with latent infection of the neoplastic B cells by the Epstein–Barr virus. Presumably such latently infected B cells arise after either clinical or subclinical infection by the Epstein–Barr virus, but their proliferation is normally held in check until there is loss of T-cell immunity after human immunodeficiency virus infection or iatrogenic immunosuppression.[10,11,51]

The pathogenesis of PCNSL occurring in immunocompetent individuals is much less understood. Human herpesvirus-8 DNA and *Toxoplasma gondii* DNA have been discovered in samples of PCNSL obtained in immunocompetent patients.[10,11,51] These data support the suggestion that chronic antigen stimulation, possibly from acquired infectious organisms, may play a role in the development of PCNSL and PIOL. Conversely, because most patients with lymphoma have some degree of reduced immunocompetence, detection of certain pathogens may simply reflect background noise or modeling inaccuracy.

Smith and colleagues[49] have identified the expression of

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the B-cell chemokine BCA-1 (also called CXCL-13) in CNS lymphoma tumors. The BCA-1 and SDF-1 molecules are lymphoid chemokines involved in B-cell compartmental homing and have been shown to be expressed in *H. pylori*–induced mucosa-associated lymphoid tissue and gastric lymphomas. Moreover, there is recent evidence that the B-cell chemokines BCA-1 and SDF-1 are expressed by the retinal pigment epithelium in patients with PIOL, suggesting a role for these chemokines in the attraction of lymphoid cells to this location from the choroidal circulation. Cell surface adhesion molecules such as LFA-1 (CD11a and CD18) and ICAM-1 (CD54) can also play a role in the homing of tumor cells to the target sites in the eye and CNS.[51]

Diagnosis of PIOL

Because PIOL is a rare disease with varied clinical features, a high index of suspicion is needed in diagnosis. Patients suspected of having PIOL should undergo a complete ophthalmic examination including slit-lamp evaluation of the anterior segment, funduscopy, fluorescein angiography, and ultrasonography whenever necessary. Fluorescein angiography demonstrates that the subretinal pigment epithelium lesions are hypofluorescent early and may reveal hyperfluorescence late in the frames (Fig. 3).[52] Ophthalmic ultrasonography is a useful adjunct to diagnosis when media opacities such as cataract and vitreous hemorrhage preclude effective visualization of the fundus. In addition, serological tests for human immunodeficiency virus, *Mycobacterium tuberculosis* (Quantiferon test), *Toxoplasma* sp, and cytomegalovirus; rapid plasma reagin and fluorescent treponemal antibody absorption tests; and angiotensin-converting enzyme levels should be obtained.[32]

Diagnostic vitrectomy should be considered in middle-aged or older patients with idiopathic unilateral or bilateral recurrent uveitis or uveitis that is unresponsive to steroid agents. Because of the importance of making the proper diagnosis and the long-term implications, treatment should not be considered without first having verified the tissue diagnosis. Even if the patient had prior known lymphoma that was then in remission in another location, if there is new onset of ocular disease, an attempt at tissue diagnosis is needed to be sure that it is not a uveitis syndrome masquerading as lymphoma. A cytological diagnosis should be made by examination of the vitreous sample obtained using fine-needle aspiration biopsy sampling or pars plana vitrectomy. Although it is the preferred approach, pars plana vitrectomy carries the risks associated with an intraocular operation, including infection, retinal detachment, vitreous hemorrhage, and cataract formation. An undiluted vitreous sample of approximately 1 ml should be collected before starting the infusion during vitrectomy. The use of topical and/or systemic corticosteroid drugs to treat idiopathic uveitis contributes to diagnostic failure because lymphoma cells frequently carry a cytoplasmic steroid receptor, and binding of the ligand triggers apoptosis with consequent cell lysis.[55] In the presence of subretinal or subretinal pigment epithelium lesions, evaluation of chorioretinal or retinal biopsy samples may increase the reliability of the diagnosis. This should be done by someone who is well versed in performing this type of biopsy procedure. Preliminary discussion of how to handle the specimen with an experienced cytopathologist and immediate processing and review of the slides may increase the chance of a correct diagnosis.[56] The evaluation of specific lymphocyte markers, including CD20, is now standard procedure.[15]

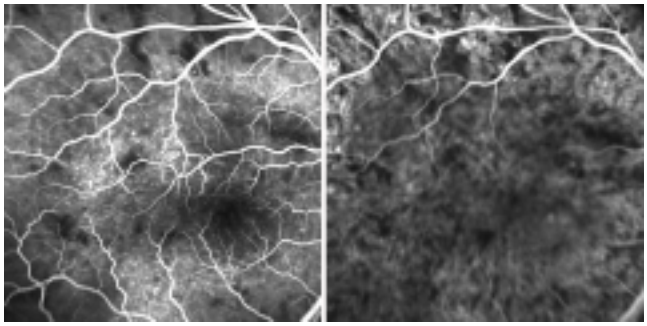


FIG. 3. Fundus fluorescein angiogram demonstrating the window-defect type of hyperfluorescence in areas of subretinal pigment epithelial infiltration *(left)*, and indocyanine angiogram demonstrating pinpoint areas of hypofluorescence corresponding to blockage of the choroidal circulation by the subretinal pigment epithelial infiltrates *(right)* in an eye with PIOL.

In addition, in certain institutions the vitrectomy specimens are also evaluated with other techniques, including κ or λ light chain restriction, flow cytometry for phenotyping, the IL-10/IL-6 ratio, microdissection for polymerase chain reaction, and gene arrangement studies. Positivity of B-cell markers (CD19, CD20) with restriction in the immunoglobulin light chains (κ or λ) is frequently observed.[10]

Interleukin-10 is a growth and differentiation factor for B lymphocytes that induces activated B lymphocytes to secrete large amounts of immunoglobulin; IL-6 is a cytokine produced by a variety of cells, including T lymphocytes, B lymphocytes, monocytes, epithelia, endothelia, and fibroblasts. Molecular analysis of ocular cytokine levels demonstrating elevation in IL-10 with an IL-10/IL-6 ratio greater than 1.0 can be a useful aid in diagnosis, although it is only confirmatory and not diagnostic.[13] The ratio of IL-10/IL-6 in the vitreous body is usually less than 1 in patients with uveitis.

Chan and colleagues[9] examined 60 cases of PIOL by using microdissection with polymerase chain reaction and gene rearrangement studies, and they demonstrated *IgH* gene rearrangements within malignant cells in all 60 tumors. The most common arrangement was at the complementary region III of *IgH*. These investigators also examined the *bcl-2* gene in 46 cases of intraocular lymphoma; in 67.4% of the samples *bcl2/IgH* gene translocation was demonstrated. The *bcl2/IgH* gene translocation results in high levels of bcl-2 protein expression, inhibiting apoptosis and causing a more aggressive disease.[10,32]

Differential Diagnosis

Any disease that causes choroidal infiltration, retinal or subretinal infiltration, or vitreous cells may mimic or be mimicked by lymphoma. That is why all forms of intraocular lymphomas are considered in the differential diagnosis of "masquerade syndromes."[22] The differential diagnosis includes all causes of chronic posterior uveitis, in-

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TABLE 2
*Differential diagnosis for PIOL**

vitreous cells alone
infectious
syphilis
endogenous endophthalmitis
Whipple disease
tuberculosis
noninfectious
sarcoidosis
pars planitis
idiopathic
CRMP-5 paraneoplastic syndrome
metastases
subretinal pigment epithelial infiltrates
infectious
retinitis
CMV, HSV, or HZV
toxoplasmosis
syphilis
Bartonella sp
nocardiosis
noninfectious
sarcoidosis

* CMV = cytomegalovirus; HSV = herpes simplex virus; HZV = herpes zoster virus.

cluding infectious causes such as syphilis, sarcoidosis, tuberculosis, cytomegalovirus, and toxoplasmosis, along with infiltrative lesions of the choroid such as metastatic tumors and amelanotic melanomas (Table 2). In lesions with vitreous cells alone, sarcoidosis, Whipple disease, tuberculosis, pars planitis, and endogenous endophthalmitis are considerations. There is a form of sarcoid uveitis that occurs more commonly in older Caucasian women that can present with dense vitreitis, cystoid macular edema, and small, deep, subretinal or choroidal lesions. These lesions may be in the far periphery and may not be seen very easily.[29] In patients with vitreitis and optic neuritis, especially in those with prior or concurrent cancer, metastatic disease or a paraneoplastic syndrome associated with CRMP-5 antibodies should also be considered (Fig. 4). In an immunosuppressed patient, disseminated choroiditis caused by *Nocardia* retinochoroiditis and *Pneumocystis* choroiditis should be excluded. Multifocal subepithelial lesions should be differentiated from diffuse unilateral subacute neuroretinitis, birdshot retinochoroidopathy, multifocal choroiditis, and punctate inner choroidopathy.

Treatment and Prognosis

Initially, WBRT was used in the treatment of PCNSL. Recurrences were common after WBRT, leading to death at a median of 12 months posttreatment.[41] Systemic high-dose methotrexate treatment in addition to WBRT prolonged the median survival duration to 33 months, from 12 months with WBRT alone. However, the combination of WBRT and chemotherapy is associated with a significant risk of neurotoxicity in elderly individuals. Neurotoxicity was diagnosed in 100% of the patients older than 60 years of age following a combined-modality approach incorporating a WBRT and high-dose methotrexate regimen.[1] The addition of high-dose methotrexate and high-dose cytosine

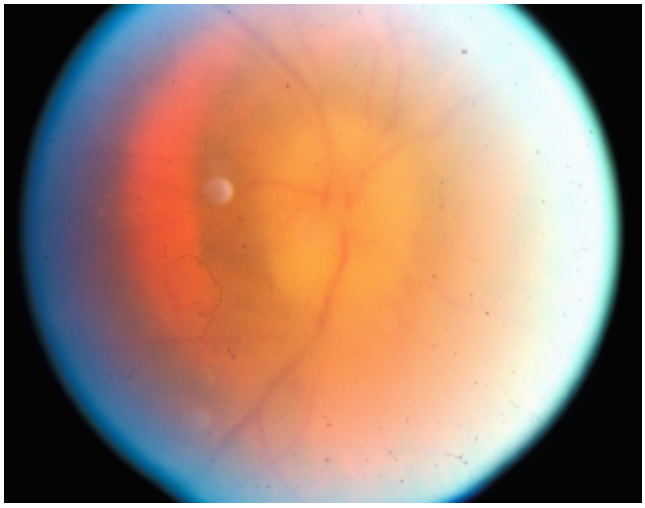


FIG. 4. Color fundus photograph obtained in a patient with CRMP-5 optic neuropathy and diffuse vitreous infiltration.

arabinoside to WBRT increased the median survival to 42.5 months.[17] Combination chemotherapy with high-dose methotrexate, cytosine arabinoside, procarbazine, and vincristine in addition to WBRT resulted in an increase of the median survival duration to 60 months.[2] There is preliminary evidence that chemotherapy without WBRT does not compromise survival in older patients. High-dose methotrexate as a single agent without WBRT yielded a median survival duration of 33 months in one series.[24] Therefore, WBRT should probably not be given in patients older than 60 years of age. There has also been debate about the usefulness of intrathecal treatment for PCNSL and PIOL. Intrathecal chemotherapy can be useful in the treatment of leptomeningeal symptoms, but high-dose methotrexate regimens without intrathecal treatment may have the same efficacy.[23,34,38] The use of bone marrow transplantation after high-dose methotrexate is also being evaluated.

Treatment of PIOL is directed at preserving the vision in the affected eye(s) and preventing CNS involvement if it is not already present. Vitrectomy improves vision by eliminating opacities formed by cellular clumps and debris in the vitreous cavity. Ocular external-beam radiotherapy, in doses of 35 to 40 Gy, has been used in the treatment of PIOL.[37] Even when one eye seems to be involved, bilateral radiation therapy is recommended because of the high incidence of bilateral disease. Radiation therapy usually causes regression of vitreous infiltrates and improvement of vision; however, recurrence and progression to CNS lymphoma are common. External-beam radiotherapy can also cause radiation keratopathy, dry eyes, cataracts, radiation retinopathy, and papillopathy. Furthermore, ocular external-beam radiotherapy does not prevent the progression to PCNSL. The overlapping radiotherapy fields in frontal lobes increase the risk of neurotoxicity if PCNSL develops subsequently. Therefore, there has been a trend in recent years away from external-beam radiotherapy and toward using systemic chemotherapy for PIOL.

High-dose methotrexate and cytarabine are the most effective agents in the treatment of PCNSL. Therapeutic levels of methotrexate have been detected in the aqueous humor of patients following systemic administration in

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doses of 8 g/m^2, but levels in the vitreous humor were comparatively lower.[28] High-dose cytarabine (3 g/m^2) achieves an effective drug concentration both in the vitreous and the aqueous humor.[5] Therefore, the presence of ocular involvement does not warrant a change in the therapeutic approach.

In the case of PIOL without CNS involvement, systemic single or combination chemotherapy as described earlier can be used.[36] The chemotherapeutic regimen is usually managed by an oncologist, hematologist, or neurologist. Ocular complications from systemic methotrexate and cytarabine are usually reversible and can be treated with topical lubricants and even topical corticosteroid agents. If the patient has refractory or recurrent intraocular disease or if the systemic therapy is medically contraindicated, local chemotherapy with intravitreal methotrexate can also be considered, as decribed later.[50] In the case of PIOL with CNS involvement, systemic therapy should be used. If refractory or recurrent intraocular disease is encountered, additional systemic/intrathecal chemotherapy with adjunctive intravitreal methotrexate is administered.[36]

There has been concern about the efficacy of systemic chemotherapy as the sole therapy in patients with PIOL. In one report, all patients with PIOL treated with systemic chemotherapy suffered recurrence.[53] Therefore, adjunctive intraocular chemotherapy or immunotherapy may be considered in patients with PIOL. Intravitreal chemotherapy with methotrexate has been found to be effective in inducing clinical remission of intraocular tumor in PIOL, with acceptable levels of morbidity. Patients were treated with (400 μg/0.1 ml) intravitreal methotrexate at the level of the pars plana. The intravitreal methotrexate injections were given twice weekly until the vitreous cavity was clinically cleared of cells. Weekly injections were then given for 1 month, followed by monthly injections for 1 year. Most eyes required four to 12 injections for tumor control.[50] In an animal model, vitreous levels of methotrexate following a 400-μg intravitreal injection remained therapeutic for 48 to 72 hours.[53] The common complications of intravitreal chemotherapy included cataract (73%), corneal epitheliopathy (58%), maculopathy (42%), vitreous hemorrhage (8%), optic atrophy (4%), and sterile endophthalmitis (4%).[50] Further treatment with intravitreal methotrexate can be given if the tumor recurs in the eye. One of the main complications of intravitreal methotrexate injection is ocular surface disease, which may be treated or prevented by topical lubricating drops, topical corticosteroid drugs, or topical folinic acid drops (leucoverin).[19]

Antibody-based treatment has become an accepted procedure in lymphomas since rituximab was approved by the Food and Drug Administration in 1997.[36] The radioimmunoconjugates ^{90}Y ibritumomab and ^{131}I tositumomab have also been approved after trials showing their efficacy in CD20$^+$ lymphomas.[33,35] Kitzmann and Pulido demonstrated that intravitreal injections of rituximab were safe and effective in the treatment of PIOL (unpublished data). Several patients have received intraocular rituximab at least once in each eye without toxicity. In addition, Pulido and Bakri have shown that following intraocular injection in rabbits, rituximab can penetrate full-thickness retina (unpublished data). This is important because in cases of subretinal infiltrates, rituximab may be able to affect these as well after intraocular injection. Further studies to determine the efficacy of this form of treatment are ongoing. Recent work supports the theory that a cytotoxic effect may be achieved using the immunotoxin BL 22, which is cytotoxic to CD22$^+$ B cells, which are found in patients with PCNSL. Further studies are required to evaluate this form of therapy as well.[20]

Despite all the improvements in diagnosis and treatment, PIOL remains an aggressive disease with an overall 5-year survival rate of less than 25%.[21] Most patients die within 2 years as a result of progressive or recurrent CNS disease.

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Address reprint requests to: Jose S. Pulido, M.D., Department of Ophthalmology, 200 First Street SW, Mayo-7, Rochester, Minne-

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