Primary Intraocular Lymphoma

An update on pathology and treatments.

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Primary intraocular lymphoma (PIOL) is a rare malignancy. It is estimated to represent less than 1% of non-Hodgkin's lymphomas and less than 1% of intraocular tumors.[1] Clinically, the disease has often been classified as a subcategory of primary central nervous system (CNS) lymphoma.[2] Recent molecular studies, however, suggest differences in disease pathogenesis.[3] Many authors have discussed the confusing nature of the PIOL terminology, and some have proposed that the disease be referred to on the basis of its origin in the retina, ciliary body, choroid, or iris.[4] PIOL is typically a high-grade B-cell malignancy.

PIOL is characterized clinically by malignant lymphocytic invasion of the vitreous, retina, or optic nerve, and may occur either as an isolated finding before involvement of the neuraxis is apparent or as a component of concomitantly or previously diagnosed CNS disease. The disease is more often bilateral, but can present asymmetrically. It is not known if the malignant transformation of these cells occurs within or outside the eye. Some authors hypothesize that the initial malignant transformation occurs outside the eye and then the malignant cells become trapped in the "immune privileged" enclosed structures of the eye, which permit tumor growth while the systemic clone is eliminated by the intact immune system. Other authors speculate that PIOL originates from lymphocytes that are chronically activated, selected, and transformed by exposure to a pathogen or antigen within the eye.

EPIDEMIOLOGY

There has been an increase in the incidence of PIOL in the older immunocompetent population over the past 20 years or so, which is not thought to be accounted for by improved neuroimaging or stereotactic neurosurgery.[5] The incidence of primary CNS lymphoma had increased over the past 30 years in part due to the increased incidence of AIDS.[5] Since the mid-1990s and increased availability of antiretroviral therapies, however, the incidence appears to have stabilized in this population of young patients.[6]

PRESENTING SIGNS AND SYMPTOMS

Patients with PIOL (Figure 1) frequently present to a retina specialist because they may manifest a variety of ophthalmic signs that can easily mimic other intraocular conditions. In a review of more than 800 uveitis patients in a large referral center, this diagnosis represented the most common masquerade syndrome accounting for one-third of all masquerade syndromes, although it represented only 1.6% of all uveitis.[7] PIOL must always be considered whenever uveitis does not

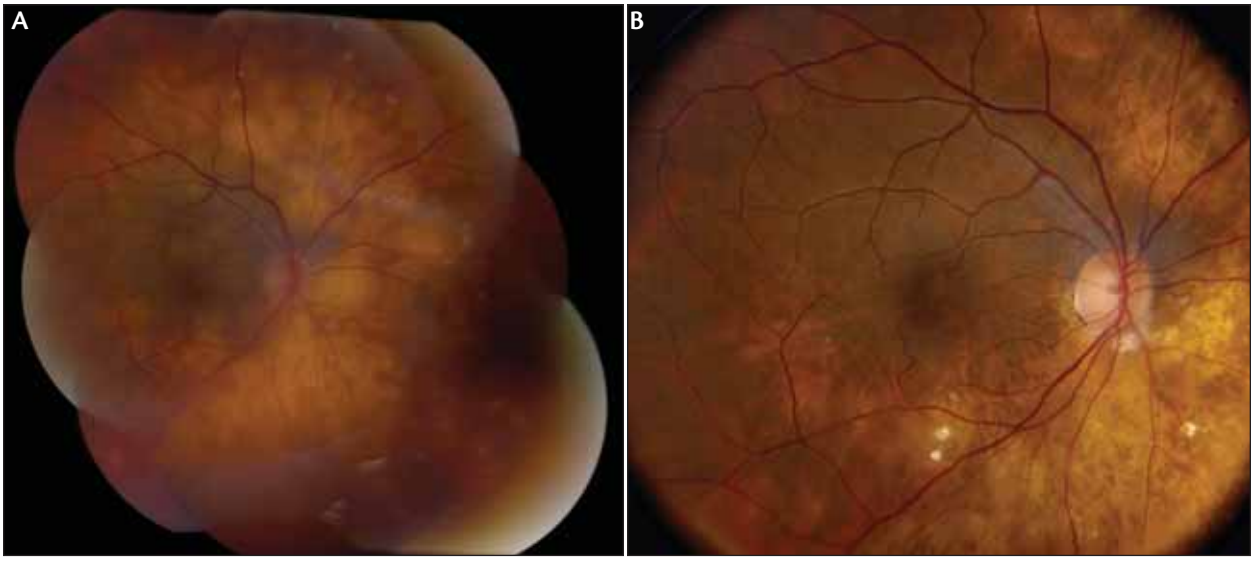

Figure 1. Montage fundus photo of the right eye of a 71 year-old Hispanic female who presented with a complaint of decreased vision in both eyes, right more than left. She had vitreous cells bilaterally as well as a mildly thickened choroid and vision of 20/80 in the right and left eyes. The patient underwent diagnostic and therapeutic vitrectomy in both eyes, which revealed a large B cell malignant lymphoma. She underwent bilateral orbital radiation therapy as well as chemotherapy with methotrexate, procarbazine, and vincristine (A). Fundus photo of the right eye 2.5 years later. The patient is 20/20 in both eyes and has remained disease-free (B).

respond to steroids in older patients.[4] Patients can present with many findings, listed in Table 1.

DIAGNOSIS

Because patients with PIOL often present with a chronic idiopathic uveitis-like presentation, definitive tissue diagnosis is often required. Pars plana vitrectomy (PPV), the most commonly used and most effective sampling technique, can provide both diagnostic and therapeutic results. The advantage of PPV is that the surgeon can obtain a large volume fluid sample and targeted tissue biopsy, facilitating cytological analysis.[2] Recently, the advent of the 23-gauge PPV system has enabled a sutureless procedure while keeping the specimen yield at least comparable with traditional 20-gauge techniques.

Most clinicians routinely send an undiluted specimen for cytology and molecular analysis with polymerase chain reaction (PCR) amplification with or without cytokine level analysis and antibody determination. Diluted vitreous specimens are typically sent for flow cytometry and bacterial/fungal/viral cultures. Even when performed properly, diagnostic vitrectomies are often negative.[8] This can occur because of minimal involvement of the vitreous or degeneration of the cells. As a result, patients often require multiple procedures before a definitive diagnosis is identified.

B-cell malignancies can secrete high levels of interleukin-10 (IL-10), an immunosuppressive cytokine, whereas inflammatory processes are associated with high levels of IL-6.[8] IL-10:IL-6 rations greater than 1 have been reported to be suggestive of PIOL and useful for following response to treatment.[9] Recently, researchers from France have reported that the measurement of IL-10 levels in aqueous can serve as a screening tool for primary intraocular lymphoma.[10] A cutoff of 50 pg/mL in the aqueous was associated with a sensitivity of 0.89 and a specificity of 0.93.

TRADITIONAL AND INVESTIGATIVE TREATMENTS

Just as it is often difficult to diagnose, PIOL is challenging to treat. Because of the blood-retinal barrier, the concentrations of drug delivered to the vitreous via intravenous injection are low and unpredictable, requiring very high dosing of the chemotherapeutic agents. Traditionally, the mainstay of treatment was external beam radiation with a 30 Gy to 45 Gy treatment prescribed to both eyes; the historical 5-year survival rates with this treatment have been dismally low at 10% to 29%.[5] Furthermore, morbidity due to neurotoxicity is common, especially in older patients, and can present as cognitive dysfunction, ataxia, and dementia.[11] Better disease control combining radiation and methotrexate-based chemotherapy has been reported,[12] but the combined strategy is not universally

TABLE 1. SIGNS AND SYMPTOMS IN PIOL[4]

Signs	Symptoms
Anterior chamber signs	Decreased vision
Anterior chamber inflammation	Floaters
Hyphema	Flashes
Hypopyon	Asymptomatic
Iris neovascularization	
Iris or angle mass	
Posterior chamber signs	
Vitritis	
Vitreous hemorrhage	
Subretinal infiltrates	
Sub-RPE infiltrates	
Retinal hemorrhage or exudates	
Perivascular infiltrate	
Retinits	
Optic disc edema	

accepted, based on retrospective surveys of routine clinical practice.[5]

Newer therapeutic strategies have included high dose chemotherapy with autologous stem cell transplantation[13] and intravitreal injections of methotrexate with or without thiotepa.[14-16] In the largest of these studies, Smith et al[16] treated 16 patients with a series of intravitreal methotrexate injections that were performed twice weekly for 1 month, then weekly for 1 month, then monthly for 1 year. Short-term remission (median, 18.5 months of follow-up) was achieved in all of the patients who completed the protocol, although six patients died of progression of intracranial disease. A major confounding factor in this study was the fact that the patients in the study received a wide range of additional treatments, including intraventricular and intravenous chemotherapy of varying regimens and ocular external beam radiation. This heterogeneity made it difficult to assess the efficacy of the intravitreal methotrexate in isolation. A group from Japan reported more recently that vitreous IL-10 levels were nondetectable after treatment in six patients treated with intravitreal methotrexate.[17] A corneal epitheliopathy was observed in all cases, which resolved after the treatment period.

Intravitreal rituximab (Rituxan, Biogen Idec/Genentech, Inc.; distributed in Europe as MabThera, Roche) is an investigational strategy that has gained attention recently. Rituximab is a chimeric monoclonal antibody directed against the B-cell specific antigen CD20 and is efficient alone or in combination with chemotherapy in systemic non-Hodgkin's lymphoma.[5,11] High doses of the drug can be safely administered intravenously in order to achieve higher concentrations in the cerebrospinal fluid.[5]

Pharmacokinetic study of intravitreal injections of rituximab in rabbits demonstrated a 4.7-day half-life of the drug in the vitreous.[18] Extrapolation of this data suggested that a 1 mg intravitreal injection of the drug in humans might deliver vitreous drug levels that would remain above 10 ng/mL for 72 days. Drugs are known to be cleared more rapidly in previously vitrectomized eyes, however, and most patients who would be eligible for this therapy have previously undergone vitrectomy and possibly cataract surgery.[18] The effect of these surgeries on the clearance of rituximab is not known. Kitzmann et al recently confirmed the lack of toxicity of intravitreal rituximab in rabbits.[19]

Kitzmann et al were also the first group to report the use of rituximab in humans. Five eyes of three patients were treated with one to four injections per eye. There were no signs of clinical toxicity, although no electroretinograms (ERGs) were performed. Clinical effectiveness of the drug could not yet be determined because all three patients in the study received either other additional ocular treatment or systemic treatment. Since this report, several other patients have been treated with success.[20] Given that 95% of PIOL malignancies are B-cell in origin and express the CD20 antigen, rituximab appears to be an ideal intravitreal therapy.

CONCLUSIONS

Primary intraocular lymphoma is a rare malignancy that is a challenge to diagnose and treat. Treatments in the past such as whole brain radiation and chemotherapy have had devastating side effects on the elderly patients whom the disease usually affects. New biological intravitreal therapies such as rituximab hold the potential promise of minimal systemic toxicity with a robust intraocular response. In the future, we are likely to see the use of combination intravitreal therapy targeted to the specific expression patterns of CD antigens for each individual patient. ■

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1. Bardenstein DS. Intraocular Lymphoma. Cancer Control. 1998;5:317–325.
2. Melson MR, Mukai S. Intraocular lymphoma. Int Ophthalmol Clin. 2006;46:69–77.
3. Malumbres R, Davis J, Ruiz P, Lossos IS. Somatically mutated immunoglobulin IGHV genes without intraclonal heterogeneity indicate a postgerminal centre origin of primary intraocular diffuse large B-cell lymphomas. British J Hematol. 2007;138:749–755.
4. Coupland SE, Damato B. Understanding intraocular lymphomas. Clin Experiment Ophthalmol. 2008;36:564–578.
5. Bessell EM, Hoang-Xuan K, Ferreri AJ, Reni M. Primary central nervous system lymphoma: biological aspects and controversies in management. Eur J Cancer. 2007;43:1141–1152.
6. Kadan-Lottick NS, Skluzacek MC, Gurney JG. Decreasing incidence rates of primary central nervous system lymphoma. Cancer. 2002;95:193–202.
7. Rothova A, Ooijman F, Kerkhoff F, Van Der Lelij A, Lokhorst HM. Uveitis masquerade syndromes. Ophthalmology. 2001;108:386–399.
8. Margolis R. Diagnostic vitrectomy for the diagnosis and management of posterior uveitis of unknown etiology. Curr Opin Ophthalmol. 2008;19:218–224.
9. Wolf LA, Reed GF, Buggage RR, Nussenblatt RB, Chan CC. Vitreous cytokine levels. Ophthalmology. 2003;110:1671–1672.
10. Cassoux N, Giron A, Bodaghi B, et al. IL-10 measurement in aqueous humor for screening patients with suspicion of primary intraocular lymphoma. Invest Ophthalmol Vis Sci. 2007;48:3253–3259.
11. Choi JY, Kafkala C, Foster CS. Primary intraocular lymphoma: A review. Semin Ophthalmol. 2006;21:125–133.
12. Ferreri AJ, Blay JY, Reni M, et al. Relevance of intraocular involvement in the management of primary central nervous system lymphomas. Ann Oncol. 2002;13:531–538.
13. Soussain C, Suzan F, Hoang-Xuan K, et al. Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. J Clin Oncol. 2001;19:742–749.
14. Fishburne BC, Wilson DJ, Rosenbaum JT, Neuwelt EA. Intravitreal methotrexate as an adjunctive treatment of intraocular lymphoma. Arch Ophthalmol. 1997;115:1152–1156.
15. de Smet MD, Vancs VS, Kohler D, Solomon D, Chan CC. Intravitreal chemotherapy for the treatment of recurrent intraocular lymphoma. Br J Ophthalmol. 1999;83:448–451.
16. Smith JR, Rosenbaum JT, Wilson DJ, et al. Role of intravitreal methotrexate in the management of primary central nervous system lymphoma with ocular involvement. Ophthalmology. 2002;109:1709–1716.
17. Sou R, Ohguro N, Maeda T, Saishin Y, Tano Y. Treatment of primary intraocular lymphoma with intravitreal methotrexate. Jpn J Ophthalmol. 2008;52:167–174.
18. Kim H, Csaky KG, Chan CC, et al. The pharmacokinetics of rituximab following an intravitreal injection. Exp Eye Res. 2006;82:760–766.
19. Kitzmann AS, Pulido JS, Mohney BG, et al. Intraocular use of rituximab. Eye. 2007;21:1524–1527.
20. Itty S, Pulido JS. Rituximab for intraocular lymphoma. Retina. 2009;29:129–132.

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