Primary Intraocular Lymphoma
With a Low Interleukin 10 to Interleukin 6 Ratio and Heterogeneous IgH Gene Rearrangement

Ronald R. Buggage, MD; Gisela Velez, MD, MPH; Brenda Myers-Powell, MD, PhD; DeFen Shen, PhD; Scott M. Whitcup, MD; Chi-Chao Chan, MD

Primary intraocular lymphoma is almost always a central nervous system B-cell non–Hodgkin lymphoma. Primary intraocular lymphoma is commonly diagnosed by demonstrating lymphoma cells in the vitreous or cerebrospinal fluid. An interleukin (IL) 10 to IL-6 ratio greater than 1.0 in these fluids and the detection of immunoglobulin gene rearrangement are useful adjuncts in the diagnosis of primary intraocular lymphoma. We report a case of primary intraocular lymphoma diagnosed by chorioretinal biopsy in which no malignant cells were identified in the vitreous and in which the IL-10 to IL-6 ratio was less than 1.0. The detection of IgH gene rearrangement heterogeneity in the tumor cells by polymerase chain reaction, a high tumor mitotic figure rate, and the rapid onset of multiple brain lesions suggest an aggressive malignant neoplasm.


Primary central nervous system (CNS) lymphoma, a non–Hodgkin lymphoma that arises in the CNS or eye, is diagnosed by identifying lymphoma cells in the cerebrospinal fluid, brain, or eye. Often the diagnosis of primary intraocular lymphoma (PIOL) is difficult because lymphoma cells may be rare and hard to recognize. Previously, we have reported that the elevation of interleukin (IL) 10 with a ratio of IL-10/IL-6 greater than 1.0 in the vitreous or cerebrospinal fluid is helpful in the diagnosis of CNS lymphoma. We report a case of PIOL confirmed by histopathologic examination, immunohistochemistry, and IgH gene rearrangement in which the vitreal cytokines showed an increase in IL-10 but a ratio of IL-10/IL-6 less than 1.0.

REPORT OF A CASE

A 40-year-old man with a history of occupational mercury exposure in 1995 developed bilateral panuveitis with retinal detachment in the left eye in April 1997. The results of a systemic workup revealed an elevated angiotensin-converting enzyme level and a decreased serum immunoglobulin level. The retinal detachment was repaired, and the uveitis resolved with systemic corticosteroid therapy. Five months later, the panuveitis recurred, and his visual acuity deteriorated to 20/40 OD and light perception OS. Lesions consistent with bilateral acute retinal necrosis were noted. The retinitis did not respond to acyclovir sodium but improved with oral corticosteroid therapy. Recurrence in January 1998 was characterized by vitritis and parafoveal exudates in the right eye. Despite the addition of methotrexate, the vitritis persisted and the retinal exudates enlarged. The results of a magnetic resonance imaging scan of the brain, a lumbar puncture, and a gallium scan showed no signs of a malignant neoplasm. By June 1998, the man's visual acuity decreased to counting fingers OD. Cyclosporine was given for 10 days. The results of a magnetic resonance imaging scan of the brain in October 1998 showed diffuse cortical atrophy compatible with mercury toxicity. A 7-day course of cyclophosphamide had little effect on the ocular disease.

The patient was examined at the National Eye Institute, Bethesda, Md, in November 1998. His visual acuity was counting fingers OD and hand movements OS with a large afferent pupillary defect. The results of the ophthalmologic examination...
tion showed bilateral conjunctival erythema and chemosis, trace keratic precipitates, anterior chamber flare, cataracts, and a depigmented left iris. There were +3 vitreous cells and haze in both eyes. Funduscop
y revealed diffuse atrophic and pigmented chorioretinal scars bilaterally and cystoid macular edema in
the right eye (Figure 1, left). The left eye had areas of subretinal fibrosis inferotemporally with foci of
creamy infiltrates (Figure 1, right). The patient underwent a diagnostic vitrectomy and a chorioretinal bi-
opsy of a creamy infiltrate in the left eye in December 1998.

The results of the chorioretinal biopsy showed a segment of detached atrophic and gliotic retina. The
subretinal space was infiltrated by macrophages mixed with numerous large atypical cells (Figure 2)
displaying at least 1 mitotic figure per high-power field. The retinal pigment epithelium was discontinu-
ous. The thickened choroid showed a predominantly T-lymphocytic infiltrate (Figure 3, left). The atypi-
cal subretinal cells stained positively with B-cell markers (Figure 3, right) and κ light chain but nega-
tively for S100 protein and keratin. The results of microdissection and polymerase chain reaction demon-
strated IgH gene rearrangements at the second and third framework regions and the third complementary
determining region of the heavy chain VDJ (V [variable], D [diversity], J [joining]) site and BCL-2 gene trans-
location in the neoplastic cells (Figure 4).

The results of a cytopathologic examination of the vitreous showed erythrocytes, lymphocytes, a few macrophages, and rare large cells with scant cytoplasm. Immunohistochemistry revealed that most cells were macrophages and T lymphocytes (Figure 5, left). Rare cells stained positively with the B-cell marker (Figure 5, right). The vitreous IL-10 level was 37 µg/mL; IL-6, 120 µg/mL.

The results of a subsequent magnetic resonance imaging scan revealed multiple CNS lesions that
were not detected 2 months before surgery (Figure 6).

COMMENT

Primary CNS lymphoma, which includes PIOL, is almost always a B-cell, non–Hodgkin lymphoma that
arises within the brain or eye. Ocular manifestations of CNS lymphoma can precede intracranial evi-
dence of the disease in 82% of cases.3 The cerebrospinal fluid and vitreous are frequently used to diagnose

Figure 1. Fundus photographs showing bilateral, diffuse, atrophic, and pigmented chorioretinal scars with macular extension and cystoid macular edema (arrow) in the right eye (left) and with creamy infiltrates in the left eye (right).

Figure 2. Left, Atypical cells with vesicular nuclei, prominent nucleoli, and a moderate rim of cytoplasm in the subretinal space (hematoxylin-eosin, original magnification ×200). R indicates retina; C, choroid. Right, High mitotic figure rate (hematoxylin-eosin, original magnification ×640).
Figure 3. CD3-positive cells in the choroid (left) and CD20-positive cells in the subretinal space (right) (avidin-biotin complex immunoperoxidase, original magnification $\times200$). R indicates retina; T, subretinal tumor; and C, choroid.

Figure 4. Polymerase chain reaction amplification showing rearrangements of the second and third framework regions (FR2A and FR3A) and the third complementary determining region (CDR3) in the VDJ (V [variable], D [diversity], J [joining]) site of the heavy chain immunoglobulin gene (IgH); translocation of the BCL-2 gene is also shown. Lane 1, patient; lane 2, negative control; and lane 3, positive control from the lymphoma cell line.

Figure 5. Many CD3-positive cells (left) and rare CD20-positive cells (right) in the vitreous (avidin-biotin complex immunoperoxidase, original magnification $\times200$).
PIOL. The diagnosis is often difficult because the lymphoma cells in these fluids may be few, and they degenerate quickly even with properly prepared specimens. Recently, cytokine analysis and detection of immunoglobulin gene rearrangement have become ancillary tools in the diagnosis of PIOL. An elevated IL-10 level relative to the IL-6 level in the vitreous and cerebrospinal fluid serves as a useful predictor of the presence of lymphoma cells, whereas an increased IL-6 level is more predictive of an inflammatory process. Gene amplification by polymerase chain reaction on cells suggestive of lymphoma microdissected from ocular tissue slides enhances the likelihood of detecting monoclonality diagnostic of B-cell malignant neoplasms.

We report a case of PIOL diagnosed by chorioretinal biopsy in which the vitreal IL-10/IL-6 ratio was less than 1.0. Several features in this case may attribute to this finding. Clinically, there were only few foci of apparently active lesions. Histologically, the tumor was confined to the subretinal space without retinal invasion. The vitreous cytologic findings demonstrated only rare lymphoma cells within a predominantly T-lymphocytic infiltrate. Such infiltrates have been reported to precede the invasion of lymphoma cells into the eye. In our case, the vitreous IL-6 level was higher than the IL-10 level, corroborating the vitreous cytologic features. Whitcup and associates found that malignant cells are significantly more likely to be present when IL-10 levels exceed IL-6 levels. The low IL-10/IL-6 ratio in this case is consistent with a lack of malignant cells in the vitreous and a low tumor volume. We believe that these features may represent an early stage of PIOL. Other potential explanations for the low IL-10/IL-6 ratio include the effect of previous immunosuppressive treatment on the tumor volume and cytokine production, vitreal sampling, and laboratory error.

The high tumor mitotic figure rate, BCL-2 gene (t14;18) translocation, multiple sites of IgH gene rearrangement detected by polymerase chain reaction, and rapid development of multiple CNS lesions all suggest an aggressive tumor course and poor prognosis. Also, the diffuse cortical atrophy may limit the clinical response to radiotherapy. This case demonstrates that in some cases of PIOL, the IL-10/IL-6 ratio may be low and malignant cells may be absent in the vitreous. In such cases, if the cause of the uveitis is obscure, a chorioretinal biopsy should be considered.

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Reprints: Ronald R. Buggage, MD, National Eye Institute, National Institutes of Health, 10 Center Dr, Bldg 10, Room 10N112, Bethesda, MD 20892-1857 (e-mail: buggage@intra.nei.nih.gov).

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