Acquired Immunodeficiency Syndrome–Related Intraocular B-Cell Lymphoma

Maria E. Rivero, MD; Baruch D. Kuppermann, MD, PhD; Clayton A. Wiley, MD, PhD; Claudio R. Garcia, MD; Mark D. Smith, MD; Anna Dreilinger, MD; William R. Freeman, MD

Objective: To present the full clinical spectrum of the acquired immunodeficiency syndrome–related intraocular lymphoma as manifested in the eye, specifically retinal lymphoma associated with primary central nervous system lymphoma, isolated ocular lymphoma, and choroidal lymphoma associated with systemic lymphoma.

Methods: Three patients with acquired immunodeficiency syndrome were noted to have atypical retinal lesions. Diagnostic retinal biopsy in 2 patients and postmortem examination of the eyes in the third case were performed.

Results: Diagnostic retinal biopsy in the first 2 patients revealed retinal B-cell lymphoma. Initial systemic evaluation showed the eyes to be the sole site of disease. Later, in 1 of these patients, the lymphoma spread to the brain. The third patient developed an acute abdomen 4 months after the development of his ocular findings. The histological evaluation of the resected bowel revealed high-grade B-cell lymphoma. The patient died 1 week later and postmortem analysis of the eyes disclosed the presence of lymphoma in the choroid of both eyes.

Conclusions: This is the most complete series of patients with acquired immunodeficiency syndrome–related intraocular B-cell lymphoma and, to our knowledge, provides the first 2 cases diagnosed by retinal biopsy. These 3 cases present the full clinical spectrum of the disease as manifested in the eye.


Neurologic disorders occur in approximately 40% of patients with the acquired immunodeficiency syndrome (AIDS) and represent the initial manifestation of the disease in approximately 10% of these patients.1,2 Toxoplasmosis and lymphoma are the most frequent central nervous system (CNS) mass lesions encountered in patients with AIDS.3

Most human immunodeficiency virus (HIV)–related lymphomas occur at an advanced stage of immunosuppression. Primary CNS lymphomas are, in most cases, seen only at autopsy. Additionally, the early clinical diagnosis of lymphoma is difficult because of the widespread spectrum of AIDS-associated diseases.4 The incidence of AIDS-associated non-Hodgkin lymphoma is estimated to be as high as 20%,5 although the eye is rarely the primary site.

Intraocular lymphoma, formerly incorrectly referred to as “reticulum cell sarcoma,” has long been known as a cause of masquerade syndrome, because the correct diagnosis is based primarily on clinical findings.5 Classically, a vitritis unresponsive to topical or periocular therapy in a middle-aged or elderly patient should be suggestive of possible intraocular lymphoma, even though the differential diagnosis of intraocular lymphoma encompasses each posterior segment disease that involves vitritis and retinal lesions.5-10 Prompt diagnosis of intraocular lymphoma is important because of its elevated association with extracranial lymphoma, either simultaneous or subsequent to ocular diagnosis.5,6,10 In patients with HIV, there is an increased risk of extranodal lymphoma in the setting of AIDS.12 The increased risk of lymphoma in all types of immunosuppression makes the proper diagnosis of this condition particularly challenging. Recently, because highly active antiretroviral therapy induced immune reconstitution, posterior segment intraocular inflammation has been described in patients with AIDS and cytomegalovirus (CMV) retinitis who have CD4+ cell elevations following treatment with protease inhibitor–containing regimens. Such intraocular inflammation (vitriris)
in the presence of retinal lesions should be considered in the intraocular lymphoma differential diagnosis.\textsuperscript{14,15}

We describe 3 patients who demonstrate the full clinical spectrum of the AIDS-related intraocular B-cell lymphoma as manifested in the eye: retinal lymphoma associated with primary CNS lymphoma, isolated ocular lymphoma, and choroidal lymphoma associated with systemic lymphoma. All 3 cases were initially misdiagnosed by experienced observers, 2 required retinal biopsy for diagnosis, while the third was an autopsy finding. To our knowledge, this is the first instance in which AIDS-related intraocular lymphoma was diagnosed by retinal biopsy. The patients were all seen at one institution and this is the most complete series of cases with AIDS-related intraocular lymphoma in which clinical documentation with fundus photography, histopathologic results, and anatomic localization are included.

**REPORT OF CASES**

**CASE 1**

A 37-year-old white man was diagnosed with HIV/AIDS in March 1990 due to *Pneumocystis carinii* pneumonia. No other HIV-related complications were noted until a diagnosis of CMV retinitis in the right eye was made in December 1991. Absolute CD4\(^+\) T-lymphocyte count at that time was 13 cells/mm\(^3\). The patient was treated with prolonged induction of ganciclovir at 5 mg/kg twice daily for 6 weeks with subsequent healing and was then given maintenance therapy. After 6 weeks, the lesions in the right eye worsened and the left eye exhibited new involvement. Anti-CMV therapy was switched to foscarnet sodium at induction of 90 mg/kg every 12 hours for 2 weeks and then to maintenance therapy at 90 mg/kg per day for an additional 2 weeks with no response. On April 21, 1992, the patient was referred to the AIDS Ocular Retina Unit at the University of California, San Diego, for consultation.

Ophthalmic examination then revealed a best-corrected visual acuity of 20/20 OD and 20/40 OS. Pupils, motility, tensions, and external examination results were unremarkable. Slitlamp examination showed cells in the anterior chamber of both eyes, 1+ in the right eye and 1+ to 2+ in the left eye. The anterior vitreous revealed cells (2+) in both eyes. Fundus examination with indirect ophthamloscopy showed substantial normal optic discs and vasculature, significant sheets of vitreous cellular debris in both eyes, and retinal lesions in both eyes (greater in the left eye). The retinal lesions were creamy in color and were associated with retinal hemorrhages and varying amounts of overlying exudative fluid. The fundus lesions involved the superior nasal quadrant in the right eye and the superior temporal quadrant in the left eye (Figure 1).

The patient underwent vitrectomy and retinal biopsy of the superior temporal lesion in the left eye (Figure 2). The eye was filled with silicone oil and, 6 weeks later, visual acuity was refracted to 20/40 OS. The vitreous biopsy specimen revealed no atypical or malignant cells or infectious organisms. The retinal biopsy specimen was layered in a gel “sandwich” and fixed in formalin as described by us previously.\textsuperscript{10} Hematoxylin-eosin–stained paraffin sections showed substantial areas of necrotic retina with collections of atypical lymphocytes locally infiltrating and expanding small vessel walls. Inflammatory infiltrates or infectious organisms were absent. Histochemical stains for fungi and acid-fast bacilli were negative. Immunostains for herpes simplex, CMV, and toxoplasmosis were also negative with appropriate controls. Immunocytochemistry for \(\kappa\) and \(\lambda\) light chain immunoglobulins showed cells staining for \(\lambda\) chain (Figure 3). The patient underwent a systemic evaluation entailing a complete physical examination, computed tomographic scans with oral contrast–enhanced views of the chest, abdomen, and pelvis, and a magnetic resonance imaging scan of the brain. The patient refused a contrast computed tomography scan of the brain, as well as a lumbar puncture. The findings of the evaluation were negative.

The patient underwent bilateral ocular radiotherapy with right and left parallel opposed portals delivering 1.80 Gy/d with a half-beam block placed anteriorly to protect the lens. From May 19, 1992, through June 24, 1992, 450 Gy was given in 25 fractions. The patient subsequently moved to a different geographic area. In November 1992, the patient complained of CNS symptoms and decreasing vision. His final ophthalmic exami-
nation was on December 2, 1992, when his visual acuity was 20/400 OD and bare light perception OS. The slit-lamp examination was reported to show pigmented keratic precipitates, which were more numerous in the left eye than the right, as well as a mild anterior chamber reaction in both eyes. Posterior synechiae were noted in the left eye. The right lens was clear, and left lens had a milky cortical and nuclear sclerotic cataract (2+). The anterior vitreous showed mild cells in the right eye. Dilated fundus examination revealed bilateral marked optic atrophy, sclerosed retinal vessels, widespread atrophic retinas, as well as zones of exudative material. The patient died 1 week later of complications related to CNS lymphoma. No postmortem analysis was performed.

CASE 2

A 49-year-old white man was diagnosed with HIV/AIDS in July 1995 when he was diagnosed with CMV retinitis in both eyes. The patient was treated with intravenous ganciclovir for 1 year before being referred to us for consultation on June 26, 1996.

Ophthalmic examination then revealed a best-corrected visual acuity of 20/16 OD and 20/20 OS. Pupils, motility, tensions, and external examination were unremarkable. Slitlamp examination showed no cells in the anterior chamber of either eye. Fundus examination revealed bilateral marked optic atrophy, sclerosed retinal vessels, widespread atrophic retinas, as well as zones of exudative material. The patient died 1 week later of complications related to CNS lymphoma. No postmortem analysis was performed.

A 49-year-old white man was diagnosed with HIV/AIDS in July 1995 when he was diagnosed with CMV retinitis in both eyes. The patient was treated with intravenous ganciclovir for 1 year before being referred to us for consultation on June 26, 1996.

Ophthalmic examination then revealed a best-corrected visual acuity of 20/16 OD and 20/20 OS. Pupils, motility, tensions, and external examination were unremarkable. Slitlamp examination showed no cells in the anterior chamber of either eye. Fundus examination revealed bilateral marked optic atrophy, sclerosed retinal vessels, widespread atrophic retinas, as well as zones of exudative material. The patient died 1 week later of complications related to CNS lymphoma. No postmortem analysis was performed.

On October 7, 1997, the best-corrected visual acuity was 20/32 OD and counting fingers OS. Ophthalmic examination revealed a panuveitis in the left eye and an advancement of the border of the retinal lesion, which was unresponsive to intravitreal cidofovir. A trans pars plana vitrectomy with retinal biopsy of the superior temporal area was performed (Figure 5) and the eye was filled with silicone oil. Visual acuity was 20/100 OS 1 month later.

Paraffin sections of the retinal biopsy specimen showed degenerate retinal tissue with underlying necrotic cells (Figure 6). Histochemical stains for organisms were negative for bacteria, fungi, acid-fast bacilli, and spirochetes. Immunocytochemical staining for CMV was also negative.

Immunohistochemical staining of the retinal biopsy specimen showed that most ghost cells had the leucocyte common antigen (CD45), the B-cell marker L26,
and, to a lesser degree, the T-cell marker CD43. UCHL-1, a pan–T-cell marker, stained only about 10% of these cells. Immunostains for light immunoglobulin chains stained for \( \kappa \) chain but not for \( \lambda \) chain, consistent with retinal lymphoma. In situ hybridization for Epstein-Barr virus RNA was negative.

A systemic evaluation entailing a complete physical examination, documentation of symptoms, laboratory evaluation (including a complete blood cell count, liver function tests, renal function tests, and an alkaline phosphatase test), chest roentgenograms, bone marrow biopsy, computed tomographic scan of the abdomen and pelvis, and a magnetic resonance imaging scan of the brain was inconclusive.

The patient was then referred for treatment with external beam radiotherapy. The source of radiation was a 6-MV photon beam and he received a dose of 4 Gy of a planed 40 Gy to the entire brain and both eyes. He tolerated his course of radiation therapy well, but he elected to forgo any additional treatment. The tumor began to regress and the visual acuity improved to 20/63 OS. The patient died 1 month later of AIDS complications, but no autopsy was performed.

CASE 3

A 35-year-old white man complained of decreased vision in the right eye in January 1992. Visual acuity was 20/400 OD and 20/20 OS. Fluorescein angiography revealed a multifocal choroiditis, which showed no improvement after 1 month of observation. The patient was treated with 60 mg/d of prednisone. Visual acuity initially improved to 20/60 OD 1 week after initiation of oral steroids, at which time the dosage was tapered. Two weeks after beginning this treatment, the vision worsened in the right eye with a notable increase in subretinal fluid. The left eye showed exudative retinal detachment and vitreous cells. The patient continued to take oral steroids for the next several weeks, while an extensive laboratory evaluation, including serum antibodies to *Toxoplasma* species, *Histoplasma* species, and *Borrelia* species, a chemistry panel, a complete blood cell count, and a thyroid panel, was performed. The results of more tests, including a computed tomographic scan of the brain and orbits as well as chest and sinus x-ray films, were normal. Pending the results of the laboratory evaluation, the patient was treated with fluconazole and doxycycline. He was then referred to us, and we examined him on April 7, 1992.

Ophthalmic examination revealed a best-corrected visual acuity of 4/200 OD and 20/50 OS. There was a right afferent pupillary defect. The anterior segment was quiet, and there were occasional anterior vitreous cells in both eyes. Dilated fundus examination revealed an inferior exudative retinal detachment with shifting fluid in the right eye with extensive pigmentary changes including areas of hypopigmentation (Figure 7). A small loculated pocket of subretinal fluid was seen along the inferotemporal arcade, and there was mild to moderate papillitis. In the left eye, a multiloculated exudative retinal detachment with moderate papillitis was observed.

On the basis of the patient's ophthalmic examination results, workup, and clinical course, as well as further information elicited from the patient that revealed a history of mild tinnitus, headache, meningism, and Native American ancestry, a tentative diagnosis of Vogt-Koyanagi syndrome was made. The dose of oral predni-
sone was increased to 200 mg/d. HLA typing was obtained and was negative for loci most typically associated with Vogt-Koyanagi syndrome (DR4, DW15). However, the clinical findings were sufficiently consistent with Vogt-Koyanagi syndrome that the patient continued to take oral prednisone, was given subtenon repository steroid injections to both eyes, and was followed up carefully for several weeks. Within 2 weeks, visual acuity had improved to 20/400 OD but had deteriorated to 3/200 OS. Three weeks later, on May 14, 1992, laboratory evaluation revealed the patient to be HIV positive, and a subsequent T-lymphocyte subset examination showed an absolute CD4+ cell count of 226 cells/mm³. By this time, the best-refracted visual acuity was 20/70 OD and light perception OS. A mild cellular reaction was observed in the anterior segments as well as the anterior vitreous. Fundus examination of the right eye revealed a complete resolution of the subretinal fluid and inflammatory choroidal exudate with extensive pigmentary change. The fundus of the left eye revealed persistent shifting subretinal fluid with a dense choroidal inflammatory infiltrate.

The next day the patient was admitted to the hospital because of abdominal pain. Systemic evaluation revealed an acute abdomen with perforated ileum requiring emergent surgical resection. Histological evaluation of the bowel revealed anaplastic large B-cell lymphoma with regional lymph node involvement. The patient died 1 week later of renal failure and pulmonary compromise. Postmortem gross analysis of the eyes revealed the presence of a mass involving the choroid. Hematoxylin-eosin–stained paraffin sections of retina demonstrated unremarkable neurosensory tissue overlying a choroid densely infiltrated by lymphoma. The choroid was expanded by a dense infiltration of anaplastic cells filling extracellular spaces and lymphatic channels (Figure 8). Immunohistochemical analysis for the B-cell marker L26 showed intense stains of the neoplastic cells. No staining was observed for the T-cell marker UCHL-1 (Figure 9). Immunohistochemical analysis of the small bowel demonstrated an identical pattern of staining (Figure 10).

**COMMENT**

Intraocular non-Hodgkin lymphoma is a well-established entity in immunocompetent patients, but seems to be very rare in HIV-infected patients. Ocular involvement can either be isolated or occur in association with CNS and/or systemic disease. Ocular involvement with non-Hodgkin lymphoma of the CNS (NHL-CNS) occurs more frequently than in association with systemic disease. In fact, isolated ocular involvement is thought to be a subset of NHL-CNS.5-7,9,10,17,18 There are some significant differences between the ocular manifestations of NHL-CNS and systemic lymphoma. Non-Hodgkin central nervous system lymphoma usually manifests as lesions in the retina, the subretinal pigment epithelial space, and the optic nerve, whereas intraocular manifestations of systemic lymphoma typically involve the uveal tract owing to inva-
sion through the choroidal circulation. Vitritis is common in both settings.

Primary CNS lymphoma can originate in the brain, spinal cord, leptomeninges, or the eye, with subsequent potential spread outside of the CNS. By contrast, systemic lymphoma, when not restricted to the lymph nodes, most commonly involves the gastrointestinal tract, bone marrow, lung, liver, or meninges, although essentially all locations have been described. Systemic lymphoma in HIV-negative patients is limited to nodal sites in more than 50% of cases. However, in AIDS-related systemic lymphoma, extranodal disease is noted in more than 80% of patients at the time of initial examination. The majority of intraocular lymphomas, regardless of whether they are due to primary CNS or systemic disease, AIDS-related or otherwise, are of high-grade B-cell origin, consisting of either immunoblastic or small noncleaved cells.

The risk for both NHL-CNS and systemic lymphomas in the setting of congenital, acquired, or iatrogenic immune suppression is 100-fold greater than in the general population. Moreover, the incidence of NHL-CNS has tripled in the last decade. This increase in the incidence of primary CNS lymphoma has paralleled the increase in the diagnosis of intraocular lymphoma in the same period. Despite this, reports of AIDS-related intraocular lymphoma are rare. In a recent autopsy series that comprised 470 eyes of 235 patients with AIDS, no cases of intraocular lymphoma were observed. Only 5 cases of AIDS-related intraocular lymphoma from 5 separate institutions have been reported in the world literature. However, none of these were diagnosed by retinal biopsy.

Our 3 cases represent the full clinical spectrum of AIDS-related intraocular lymphomas manifested in the eye. In the first and second cases, the retinal biopsy specimen revealed intraretinal infiltration with lymphoma-tous cells. Systemic workup showed no sign of extra-CNS lymphoma, consistent with a subset of primary CNS lymphomas in which involvement is restricted to the eye. The retinal involvement is the most common pattern for primary CNS lymphoma associated with ocular manifestation, although choroidal disease may also occur. In fact, the first patient died of CNS lymphoma. Clinically, the first 2 cases were initially confused with CMV retinitis and, after repeated and unsuccessful anti-CMV treatments, a chorioretinal biopsy led to the correct diagnosis. In contrast, the third patient was diagnosed shortly before his death with gastrointestinal lymphoma. Postmortem analysis of his eyes confirmed the presence of lymphomatous infiltration restricted to the choroid, typical of ocular involvement in systemic lymphomas. Radiologic workup showed no CNS involvement.

In summary, these 3 cases highlight the challenge in making a prompt and accurate diagnosis of this complex disease entity. The fact that the intraocular lesions can be a manifestation of either systemic, primary CNS lymphoma, or isolated ocular lymphoma and thus involve distinct intraocular structures adds difficulty in diagnosing HIV-infected patients. Results of cytopathologic examination of vitreous biopsy specimens alone may be insufficient in diagnosing in intraocular lymphomas, subsequently documented by CNS biopsy.

In the setting of atypical retinal pathology or failure of antiviral therapy in patients with AIDS, a retinal biopsy of the lesion may be the necessary diagnostic approach. The tendency of intraocular lymphoma to mimic other diseases, the multicentricity of primary ocular CNS lymphoma, and the poor prognosis for patients with AIDS with untreated lymphoma suggest that early and accurate detection of intraocular lymphoma may be beneficial not only for early treatment of eye disease but also for CNS disease, the latter being the source of significant mortality. Retinal biopsy of the lesions is more likely to provide an accurate and prompt diagnosis of this and other atypical posterior segment pathologic entities associated with AIDS.

Accepted for publication December 21, 1998.

This investigation was supported in part by grant EY07366 from the National Eye Institute, National Institutes of Health, Bethesda, Md (Dr Freeman), the Ronald G. Michels Foundation, Baltimore, Md (Dr Kuppermann), and a department grant from Research to Prevent Blindness Inc, New York, NY (Dr Freeman).

Reprints: William R. Freeman, MD, Shiley Eye Center, 9415 Campus Point Dr, La Jolla, CA 92039-0946.

REFERENCES

6. Qualman SJ, Mendelson G, Mann RB, Green WR. Intraocular lymphomas: natural history based on a clinicopathologic study of eight cases and review of the

©1999 American Medical Association. All rights reserved.


From the Archives of the Archives

K NAPP (New York) described in his Recent experiences with cataract operations, 1050 in number, of which the last 400 included all complicated cases. The method of operation was usually a simple extraction without iridectomy, and the incision at the border of the transparent cornea, almost half its extent. The capsule was opened with the cystome to the extent of five or six mm in the upper part underneath the iris, so that the torn pupillary edge of the iris and the wounded capsule should not touch. Pressure at the lower part of the cornea easily delivers the lens, but contact of the border of the lid and the corneal wound should be avoided. Both eyes are bandaged afterwards, and the dressing changed after twenty-four hours. In 355 operations prolapse of the iris occurred fifteen times (7.6%) and was successfully treated by iridectomy. Secondary operations were done in 40% of the cases. In three cases, glaucoma following discission was observed. Recovery was obtained by means of iridectomy, cataract, and morpheine.