

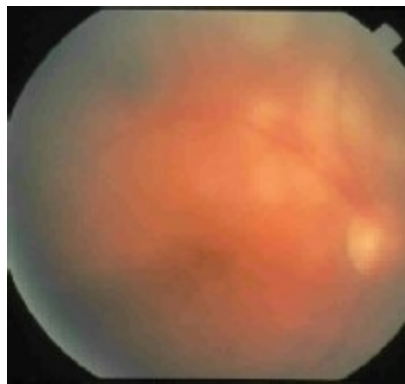
## OCULAR LYMPHOMA

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### CASE

The patient is a 44 year old man who first noted decreased vision in the left eye in October 93, then in the right eye in January 94. He was examined by his ophthalmologist, who told him that he had "retinal inflammation and swelling." He was treated with prednisone 60 mg a day, and prednisolone acetate 1% every hour in both eyes. His vision improved minimally with the treatment. He also had numerous blood tests and a chest X-ray, which reportedly were all within normal limits. He was examined by a neuro-ophthalmologist, and had an MRI of the brain, which was also normal.

The patient was referred in March 1994. The patient's visual acuity at the time was counting fingers OD, and 20/40 OS. The anterior segment exam and intraocular pressures were within normal limits. Biomicroscopy revealed 3+ vitritis OD, and 1+ vitritis OS. The examination of the right fundus showed a hazy media, some attenuation of the retinal vessels, and multiple creamy yellow-white lesions at the level of the RPE, superior to the optic disc and in the superior arcades. (Fig. 1)



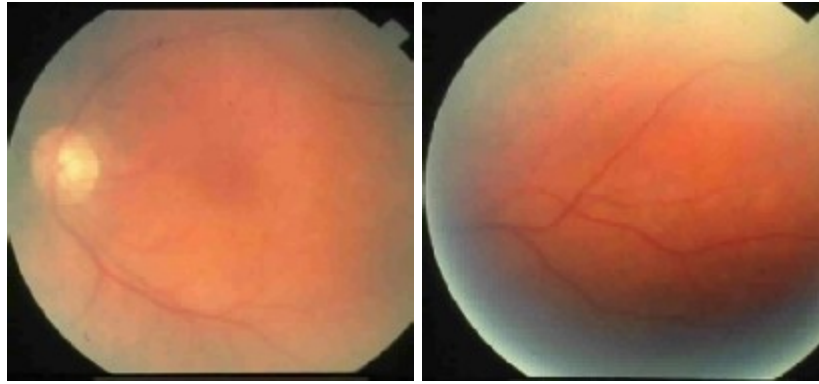
**Figure 1**

These lesions were also found scattered nasally and inferiorly to the optic disc. (Fig. 2)



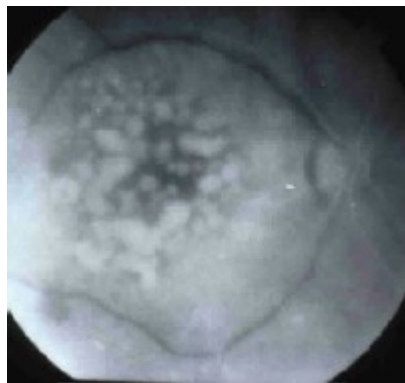
**Figure 2**

In the left eye multiple small yellow lesions were present throughout the posterior pole. (Figs. 3 & 4)



**Figure 3 \*\*\*\*\* Figure 4**

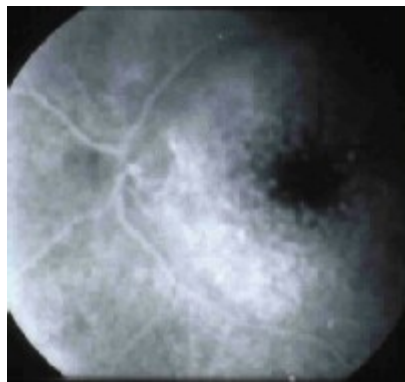
Fluorescein angiogram of the right fundus showed areas of hyperfluorescence in the central macula and superior to the disc, which corresponded to some of the lesions noted on exam. (Fig. 5)



**Figure 5**

Late frames of the angiogram showed persistence of the hyperfluorescence.

Fluorescein angiogram of the left fundus revealed multiple punctate hyperfluorescent lesions seen in the posterior pole. (Fig. 6)



**Figure 6**

These lesions remained stable throughout the angiogram.

The patient's past medical history was significant for testicular cancer at age 2, which was treated in Poland with orchiectomy and radiation therapy. Social history disclosed that he was a chemist and traveled to several foreign countries. He grew up on a farm with cows, pigs and chickens. He enjoyed raw meat and deer hunting. In the recent past, he skinned his own deer without gloves. He also was a cat owner.

The immunologic workup was significant for a white blood cell count of 15,700, and a markedly positive PPD, although he did receive BCG in childhood. Serologic tests were significant for a positive varicella IgG, with a negative IgM. Hepatitis A IgG was positive with a negative IgM, consistent with past infection. Other serologic tests

including herpes simplex, toxoplasmosis, toxocara, Lyme disease, FTA-abs, cat-scratch disease, tularemia, cryptococcus, histoplasmosis, and cysticercosis were all negative.

The patient was treated with IV acyclovir for presumed acute retinal necrosis. However his vision in the left eye deteriorated to 20/100 despite the treatment. Multifocal choroiditis was suspected and the treatment was changed to Cyclosporin and Imuran, along with Rifampin and INH, given the markedly positive PPD. Diagnostic vitrectomy was delayed due to an acute viral conjunctivitis. Sulfadiazine and pyrimethamine were further added to the treatment regimen by the Infectious Disease consultants for possible toxoplasmosis, despite the negative antibody titers. The patient underwent a diagnostic vitrectomy of the right eye in April 1994. Cytologic study of the vitreous specimen revealed markedly atypical lymphoid cells suspicious for lymphoma. (Fig. 7)

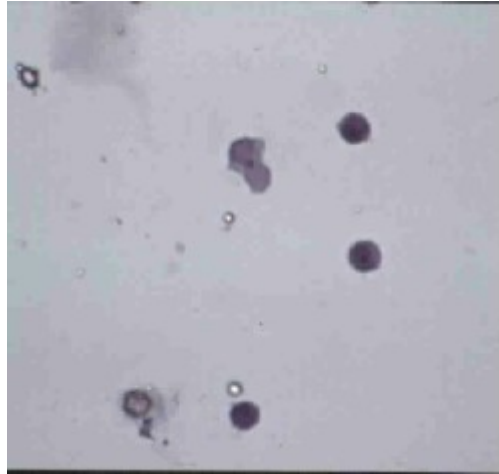


Figure 7

A complete neurologic workup including neurologic history and physical exam, lumbar puncture with cytology of the CSF, and MRI of the brain were all negative. In May, the patient's vision further decreased to counting fingers ou. Radiation therapy was instituted. Vision improved to 20/500 OD, and 20/300 OS, and the deep retinal lesions began to regress. (Fig. 8)



Figure 8

A year later the patient started experiencing memory loss. An MRI of the brain showed a large mass in the splenium of corpus callosum. (Fig. 9)

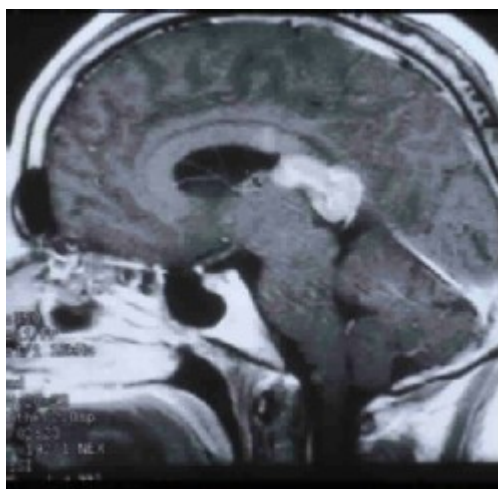


Figure 9

Brain biopsy of the lesion revealed CNS B-cell lymphoma. The patient was treated with chemotherapy and radiation therapy.

#### DISCUSSION

Non-Hodgkin's lymphoma of the central nervous system (NHL-CNS) (previously called reticulum cell sarcoma), may also properly be referred to as intraocular large cell lymphoma. Reticulum cell sarcoma is a misnomer, since the tumor is neither a sarcoma nor comprised of reticulum cells. The incidence of Non-Hodgkin's lymphoma of the central nervous system has slowly increased since 1960, and has trebled over the past 15 years. (1) This increase cannot be fully explained by AIDS or other causes of immunosuppression. The median age is between 50 and 60 years. There is a slight male predominance. Three populations are at risk of developing NHL-CNS: patients with AIDS; transplant recipients; and patients with congenital immunodeficiencies, such as Wiskott-Aldrich syndrome and severe combined immunodeficiency.

Patients with NHL-CNS can present with four distinct profiles: solitary or multiple discrete intracranial nodules, diffuse meningeal or periventricular lesions, subretinal infiltrates or vitritis, and localized spinal masses. (1) Ocular involvement may precede disease in other parts of the CNS. Both Whitcup and Freeman reported only half of their patients had CNS lesions on neuroradiologic studies by the time intraocular lymphoma was diagnosed. (2,3) Freeman also reported ocular symptoms preceded CNS symptoms in 82% of patients with CNS disease. The mean time between the onset of ocular symptoms and the onset of CNS symptoms was 29 months. (3)

The most common presenting ocular symptoms are blurred vision and floaters. Pain and conjunctival hyperemia are rare. Vision is often decreased. Biomicroscopic exam often shows mild anterior segment inflammation with cells and flare and keratic precipitates. Vitreous cells occurring in sheets are characteristic. Although the disease may begin with one eye, bilateral involvement is common after several months. Fundus examination often shows subretinal yellow infiltrates. Many atypical fundus presentations have been reported, including hemorrhagic retinal vasculitis, and hemorrhagic retinal necrosis. (4,5) Multiple RPE detachments have been described by Gass as being pathognomonic. (6) Exudative retinal detachments, thickening of the uveal tract (7) and papillitis have all been described. Intraocular lymphoma should be suspected when chronic uveitis is poorly responsive to corticosteroids, and when there is a characteristic vitritis with deep retinal lesions. The vision is often better than expected based on the clinical examination.

All patients suspected of having intraocular lymphoma should undergo a neurologic workup. Neurologic symptoms such as headache, focal weakness, sensory deficits, confusion, personality change, and difficulty with gait may be present. A history of recent seizure is also a strong indication of CNS involvement. The neurologic workup should include an MRI of the brain, and lumbar puncture with examination of the CSF. The cytology of CSF is diagnostic of course if it is positive. Since lymphoma cells are fragile, it is important that samples be immediately transported to the cytology laboratory for processing. At least 10 cc's of CSF should be sent. A repeat lumbar puncture may be necessary for the diagnosis.

If the CSF shows no malignant cells, a pars plana vitrectomy on the eye with the most severe vitritis or the worst vision is the next step. Char demonstrated loss of cellular detail when the vitreous specimen was obtained through vitrectomy cutter, and therefore he advocates aspiration of 1 cc of vitreous, with or without cutting depending on the ease of aspiration, prior to vitrectomy. (4) The vitreous specimen should be handled with care and immediately carried to the cytology lab. Tissue culture medium enriched with 10% fetal calf serum can be added to the collection

chamber of the vitrectomy machine to improve cell viability. Multiple vitrectomies may be needed to make the diagnosis of intraocular lymphoma. Char and colleagues reported 3 of 14 patients required more than one vitrectomy.(8) Whitcup and colleagues reported 3 of 10 patients had one or more negative vitrectomies before the diagnosis was made.(2) Mishandling of the vitreous specimens may partially account for the false negative diagnostic results. However, treatment with corticosteroids also may be responsible for the paucity of viable lymphoma cells in vitreous specimens. Steroids can be cytolytic to CNS lymphoma cells. The sensitivity of the tumor cells to corticosteroids is unique to CNS lymphoma and is not seen with any other CNS malignancies. This sensitivity to steroids contributes to the difficulty in diagnosing this disease, since many patients with intraocular lymphoma are treated with corticosteroids at the time of vitrectomy for presumed chronic uveitis.

Typical lymphoma cells are large and pleomorphic with scanty cytoplasm. The nuclei are round and hypersegmented with prominent nucleoli. Unlike systemic lymphomas that invade the choroid, most of CNS lymphoma cells are located between the RPE and Bruch's membrane. (Fig. 13) Chorioretinal biopsies have been used to diagnose intraocular lymphoma in some cases.(9) However, the risks of biopsy are significant, and the sensitivity is unclear. Immunohistochemical staining may be helpful by detecting monoclonal B cells with a kappa or lambda light chain, and can confirm the diagnosis.(10,11) However since tumor cells are mixed with inflammatory cells, immunologic analysis often reveals lymphocyte heterogeneity, making the study less reliable than cytology.

Interleukin-10 is a growth and differentiation factor for B lymphocytes. Recently Chan and colleagues measured IL-10 levels in vitrectomy specimens from 3 patients with intraocular lymphoma and 5 patients with uveitis.(12) In their report, IL-10 was detected in the vitreous of all 3 patients with intraocular lymphoma, but in none of the vitreous specimens of the patients with uveitis. They also demonstrated the levels of IL-10 in the vitreous correlated with both severity of vitritis and numbers of malignant cells by cytology. Given the difficulty of diagnosing intraocular lymphoma accurately, IL-10 in the vitreous may provide a helpful diagnostic clue.

Treatment consists of radiation therapy, and combined radiation therapy and chemotherapy if CNS disease is present.

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## REFERENCES

1. Hochberg FH, Miller DC. Primary central nervous system lymphoma. *J Neurosurg* 1988;68:835-853.
2. Whitcup SM, deSmet MD, Rubin BI, et al. Intraocular lymphoma: Clinical and Histopathologic diagnosis. *Ophthalmology* 1993;100:1399-1406.
3. Freeman LN, Schachat AP, Knox DL, et al. Clinical features, laboratory investigations, and survival in ocular reticulum cell sarcoma. *Ophthalmology* 1987;94:1631-9.
4. de Smet MD, Nussenblatt RB, Davis JL, Palestine AG. Large cell lymphoma masquerading as a viral retinitis. *Int Ophthalmol* 1990;14:413-17.
5. Ridley ME, McDonald HR, Sternberg P Jr, et al. Retinal manifestations of ocular lymphoma (reticulum cell sarcoma). *Ophthalmology* 1992;99:1153-61.
6. Gass JDM, Sever RJ, Grizzard WS, et al. Multifocal pigment epithelial detachments by reticulum cell sarcoma. A characteristic fundoscopic picture. *Retina* 1984;4:135-143.
7. Duker, JS, Shields, JA, Ross M. Intraocular large cell lymphoma presenting as massive thickening of the uveal tract. *Retina* 1987;7:41-45.
8. Char DH, Ljung B, Miller T, Phillips T. Primary intraocular lymphoma (ocular reticulum cell sarcoma): Diagnosis and management. *Ophthalmology* 1988;95:625-630.
9. Kirmani MH, Thomas EL, Rao NA, Laborde RP. Intraocular reticulum cell sarcoma: diagnosis by choroidal biopsy. *Br J Ophthalmol* 1987;71:748-752.
10. Char DH, Ljung B, Deschenes J, Miller TR. Intraocular lymphoma: immunological and cytological analysis. *Br J Ophthalmol* 1988;72:905-911.
11. Ljung B, Char DH, Miller TR, Deschenes J. Intraocular lymphoma: cytologic diagnosis and the role of immunologic markers. *Acta Cytol* 1987;32:840-847.
12. Chan C, Whitcup SM, Solomon D, Nussenblatt, RB. Interleukin-10 in the vitreous of patients with primary intraocular lymphoma. *Am J Ophthalmol* 1995;120:671-673.