Could it be Intraocular Lymphoma?

Ocular involvement should be considered as one manifestation of CNS lymphoma.

BY DAVID J. WILSON, MD

Intraocular lymphoma remains one of the greatest masqueraders among retinal diseases. For example, figure 1 shows a variety of the presenting clinical features in five patients with intraocular lymphoma. Perhaps of even greater challenge, however, are the questions that arise in treating a patient with intraocular lymphoma. Intraocular lymphoma often requires the ophthalmologist to adjust the treatment of coexisting ocular symptoms to complement systemic therapy for the cancer and to address visual disturbances.

Intraocular lymphoma can be divided into primary central nervous system (CNS) lymphoma and primary uveal lymphoma. Primary CNS lymphoma is the subject of this article.

DEFINITIONS

Lymphoma. Lymphoma is a malignant neoplasia of white blood cells of lymphocytic origin. Lymphomas may be derived from B or T lymphocytes, but the lymphomas that affect the eye are primarily of B-cell origin.

Primary CNS lymphoma (PCNSL) or primary vitreoretinal lymphoma. PCNSL is a subgroup of lymphoma that characteristically involves the brain, eyes, and leptomeninges without other systemic involvement. This is most commonly a B-cell lymphoma, but rare cases of T-cell PCNSL have been reported. This lymphoma is high grade and is generally classified as a diffuse large B-cell lymphoma (DLBL). This type of lymphoma will be discussed in this article.

Primary uveal lymphoma. This rare form of lymphoma affects the uvea and is distinctly different from PCNSL. Primary uveal lymphoma is generally a low-grade lymphoma of B-cell origin. In primary uveal lymphoma, the uvea is the primary site of involvement: ie, there is no systemic lymphoma at the time of diagnosis. This type of intraocular lymphoma is not discussed in this article.

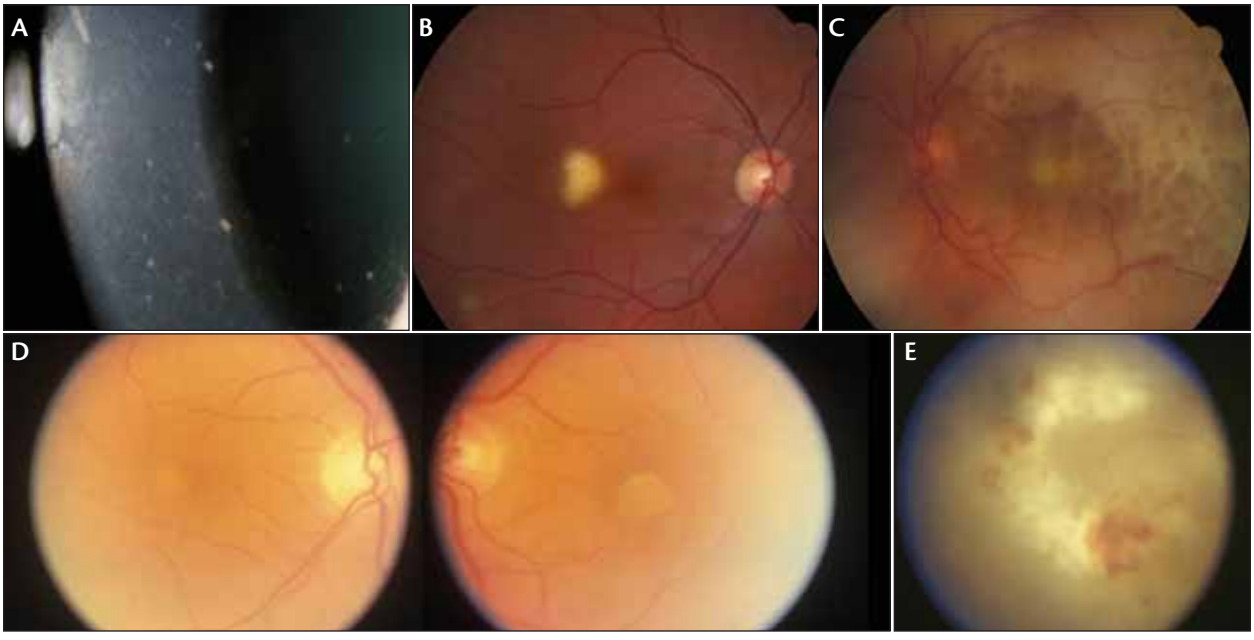

Figure 1. Keratic precipitates in a patient with PCNSL. Note the dendritiform character of the precipitates (A). Typical sub-RPE deposit in a patient with PCNSL (B). Extensive subretinal and sub-RPE deposits in a patient with PCNSL (C). Bilateral macular sub-RPE deposits in a patient with PCNSL (D). PCNSL presenting as ischemic retinopathy (E).

CLINICAL PRESENTATION

Uveitis. The majority of patients with intraocular lymphoma will present with anterior or posterior uveitis. In one large series of intraocular lymphoma, 75% of patients presented with either anterior or posterior uveitis. In this same series, the pathognomonic feature of PCNSL, subretinal pigment epithelial (sub-RPE) infiltrates were present in only 20% of patients. At times, the keratitic precipitates associated with PCNSL will have a branching, dendritiform appearance (Figure 1A).

Sub-RPE Infiltrates. Sub-RPE infiltrates are the most distinct feature of PCNSL. These infiltrates are due to the accumulation of atypical lymphocytes beneath the RPE. These infiltrates vary in thickness and size (Figure 1B to D). They are usually, but not always, accompanied by cells in the vitreous cavity. Even without treatment, these subretinal infiltrates may come and go. When they resolve after being present for some time they typically leave an area of geographic atrophy.

Ischemic retinopathy or optic neuropathy. In some patients, atypical lymphocytes will accumulate within and around the retinal vessels. The resulting vascular compromise gives the clinical appearance of ischemic retinopathy (Figure 1E). Cases presenting in this fashion are often misdiagnosed as viral retinitis.

DIAGNOSIS

PCNSL should be suspected in any patient with posterior uveitis who has a negative workup for common causes of posterior uveitis. PCNSL is often partially responsive to oral or periocular steroids but will tend to recur or worsen after an initial response. Consequently, PCNSL should be considered in patients with this clinical course. When PCNSL is considered, the diagnosis may be confirmed in a variety of ways: cytology, immunophenotyping, assessing for gene rearrangement, and assaying for cytokines in ocular fluids.

Cytology. Cytology of cells removed from the vitreous or aqueous is the most common method for making a diagnosis of PCNSL (Figure 2). The atypical cells that are present in this disease have a characteristic appearance, as they are larger than normal lymphocytes, and have nuclear features that are typical for lymphoma. The atypical cells usually occur intermixed with normal inflammatory cells, so the cytologist must look for a subpopulation of cells with the features of lymphoma. In addition to the normal and atypical lymphocytes, there is often a population of necrotic cells. The presence of these necrotic cells is often a clue that the cellular infiltrate is due to lymphoma rather than a benign inflammatory process.

Immunophenotyping. Immunophenotyping is a powerful technique to characterize cells removed from the vitreous on the basis of the presence of identifiable surface proteins. For example, the cells can be identified as B- or T-cells, and the number with kappa or lambda light chains can be identified. This information complements the findings on cytology, and can help confirm that there is a subpopulation of atypical cells that exhibit "clonality": that is, that they all share the same surface light chain.

Gene Rearrangement. This technique, like immunophenotyping, is helpful in identifying clonality within the cells removed from the ocular fluids. Whether to use immunophenotyping or gene rearrangement studies depends on the experience of a particular pathology laboratory; some labs use both.

Cytokine Ratio. Assays of the amounts of interleukin 6 (IL6) and interleukin 10 (IL10) have been used to distinguish benign intraocular inflammatory conditions from PCNSL. In benign infiltrates, the IL10:IL6 ratio is typically less than 1, whereas in PCNSL it is typically greater than 1. There is some overlap between the different types of infiltrates and some variation in ratios obtained in different laboratories; however, this ratio may be useful in initial diagnosis and in follow-up for recurrences.

TREATMENT

Systemic therapy. As mentioned above, retinal or vitreous involvement alone or in combination with brain or leptomeningeal lymphoma is PCNSL, a subtype of DLBL. This is a high-grade lymphoma that is treated with systemic combination chemotherapy. Treatment of eye involvement should be performed in conjunction with a neuro-oncologist or medical oncologist. Prior to initiation of therapy, patients should undergo a staging evaluation to document the extent of involvement. This should include lumbar puncture and neuro-imaging to define the extent of disease at presentation.

There are a variety of chemotherapy regimens for DLBL, the vast majority of which include high-dose methotrexate in combination with other agents. Increasingly, rituximab (Rituxan, Genentech), a chimeric antibody that recognizes and induces apoptosis in CD20-positive cells (B-cells), is used in the chemotherapy regimen for patients with DLBL. CNS involvement develops in 80% to 90% of patients who initially present with vitreous and retinal involvement, so systemic therapy should be strongly considered even in the treatment of patients who have only eye disease at initial staging.

Gene expression studies indicate that PCNSL is a distinct type of DLBL, differing in some aspects of gene expression from the better known germinal center cell and activated B-cell subtypes. The 5-year disease-free survival rates vary widely in these two forms of DLBL, with 70% survival for germinal center cell type and 30% for the activated B-cell type. Gene expression studies and survival rates for PCNSL are more similar to the rates seen in the

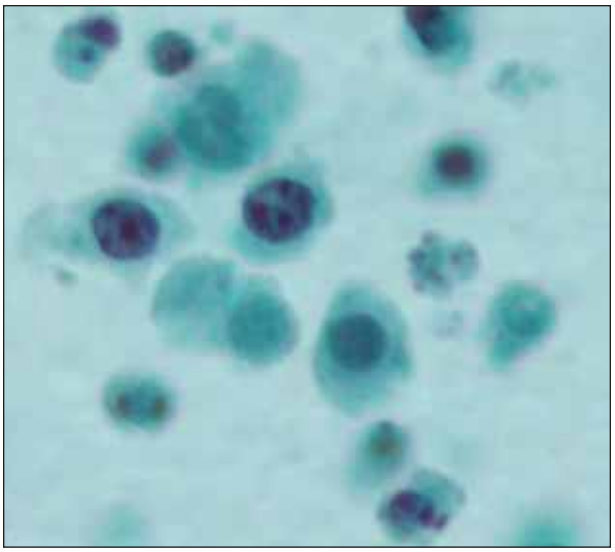

Figure 2. Cytology of PCNSL. The lymphoma cells are large cells with condensed chromatin and prominent nucleoli. There are also numerous cell ghosts or necrotic cells.

activated B-cell type, indicating that PCNSL has a poorer prognosis and that it is very likely that there will be recurrence of disease at some time following initial treatment.

Ocular therapy. As previously mentioned, ocular therapy should be considered in the context of the type of systemic therapy that is being delivered to the patient. If the patient is receiving high-dose systemic chemotherapy, the eyes may be observed for response. Many systemically administered agents reach therapeutic levels in the ocular fluids, so if the intraocular involvement responds to systemic therapy, there is no need to administer additional treatment. If the ocular involvement does not respond to systemic therapy, chemotherapy may be administered by intravitreal injection. The two most commonly utilized agents are methotrexate and rituximab. These two agents appear to be well tolerated, with minimal drug-related toxicity. When these are used in combination with systemic therapy, it is logical to treat the eyes with the intent to induce complete remission. This can be achieved in an extremely high number of patients with methotrexate alone or in combination with rituximab.

For a high percentage of patients, the medical or neuro-oncologist will elect not to treat with systemic chemotherapy. In many elderly patients with no brain or leptomeningeal involvement, the side effects of therapy may be considered to outweigh the benefits of treatment in the absence of life-threatening manifestations of the disease. In this setting, the treating ophthalmologist must decide whether to treat the eyes alone. This decision should rest on the patient's visual symptoms and the threat the ocular involvement poses for permanent vision loss. If the vitreous infiltrate is sufficiently dense to lower vision, vitrectomy will generally return vision to a near-normal level. Intraocular chemotherapy is also effective in clearing the vitreous of cells, resulting in visual improvement. If there are extensive subretinal infiltrates, particularly if they threaten the fovea, the use of intravitreal chemotherapy is generally effective in eliminating the infiltrates. Also, in settings of ischemic retinal or optic nerve disease, the use of intravitreal chemotherapy is effective in removing the cells from the vitreous and retina.

With systemic chemotherapy alone or in combination with intraocular therapy, there is a high risk of recurrent disease, so patients must be followed indefinitely for signs of recurrence.

Radiation therapy. Radiation therapy is currently used much less frequently than in the past. Whole-brain radiation in conjunction with chemotherapy in older patients is now recognized to be associated with a high incidence of severe dementia and little improvement in survival compared with chemotherapy alone. Use of radiation to the eyes of patients with ocular involvement can be considered, but the dose used for treatment will be associated with a substantial risk of radiation retinopathy and will result in some radiation to the brain also.

CONCLUSION

Intraocular lymphoma is a disease with protean manifestations. Ocular involvement should be considered one manifestation of CNS lymphoma, and patients should be treated with systemic chemotherapy alone or in combination with intraocular chemotherapy. ■

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