

ONCOLOGY

Demystifying Ocular Lymphoma

BY LORI BAKER-SCHENA, EDD, MBA, CONTRIBUTING WRITER

INTERVIEWING HANS E. GROSSNIKLAUS, MD, MBA, ARUN D. SINGH, MD, AND DAVID J. WILSON, MD

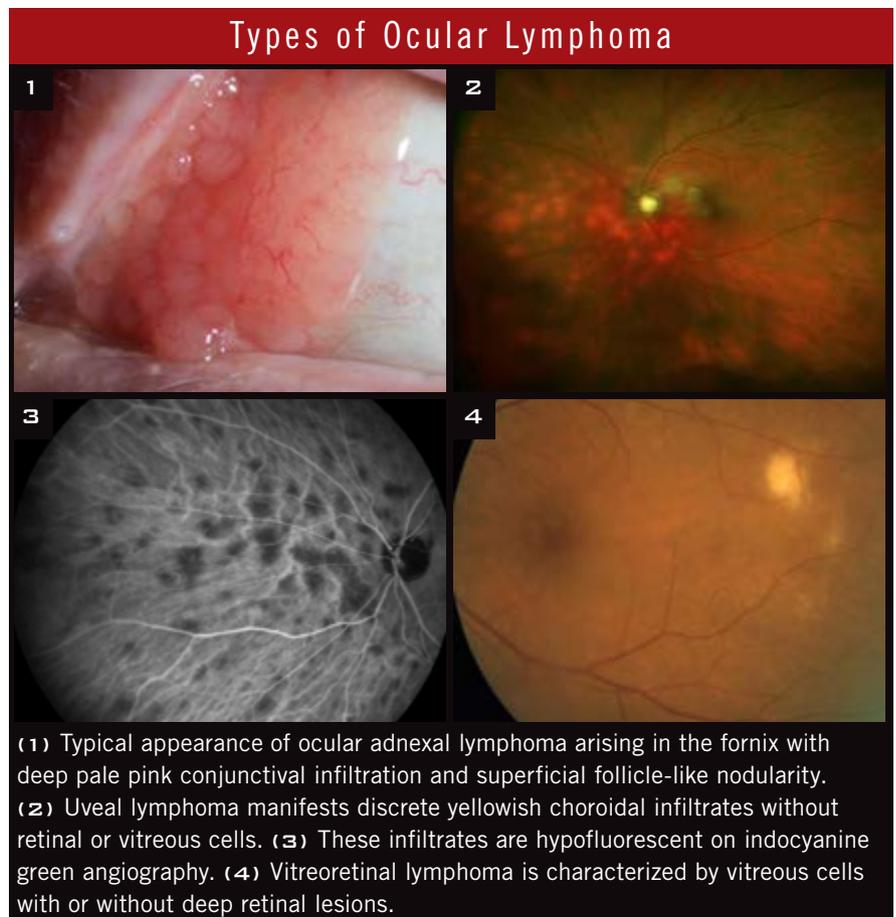
Intraocular and ocular adnexal lymphomas are rare, diverse, and often confounding. A differential diagnosis can be tricky, as many of these patients present with uveitis and intraocular inflammation—common clinical features. Biopsy techniques are specialized, and treatment requires a multidisciplinary team of ocular oncologists, general oncologists, pathologists, and radiation oncologists.

Yet for all their complexity, intraocular and ocular adnexal lymphomas are not only manageable, but survivable. Recent advances in tumor biology are leading to more targeted therapies, which is why recognizing and treating this disease is vital.

“There is a common assumption that patients with ocular and central nervous system (CNS) lymphomas do not live long,” noted David J. Wilson, MD, at Oregon Health & Science University. “Yet most of these patients have a long survival. Consequently, treatment must be designed to preserve patients’ visual acuity and maintain their eye in a functional state.”

An Ocular Lymphoma Primer

According to Arun D. Singh, MD, at the Cleveland Clinic, demystifying ocular lymphomas begins with a working knowledge of the disease. “The first point to recognize is that ocular lymphoma can be localized or systemic disease,” he explained. “Second, it is multifocal in origin; lymphoma can arise in other sites in the body without



metastasizing.”

Lymphomas can be divided into three groups—ocular adnexal, uveal, and vitreoretinal—and each type differs in its clinical presentation, diagnosis, treatment, and outcomes.

Ocular adnexal. Ocular adnexal lymphomas involve the eyelid, conjunctiva, lacrimal gland, or other orbital structures. Dr. Singh noted that the majority are low-grade, B-

cell, non-Hodgkin lymphoma, and approximately 80 percent are of the extranodal marginal zone lymphoma histologic subtype. Findings from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program indicated that the incidence of ocular adnexal lymphoma rose at an annual rate of 6.3 percent between 1975 and 2001.¹

Uveal. Similar to ocular adnexal,

uveal lymphoma is typically a non-Hodgkin lymphoma, most frequently of B-cell origin, Dr. Singh said. Uveal lymphoma can be divided into primary or secondary; the latter is a manifestation of systemic lymphoma. Primary uveal lymphoma can be further subdivided into choroidal, iridal, and ciliary body lymphoma. The majority of cases are primary choroidal lymphoma and are generally low grade, with a prolonged, indolent course.

Vitreoretinal. In contrast, vitreoretinal lymphoma, also known as primary intraocular lymphoma, is a variant of primary CNS lymphoma and is usually a diffuse large B-cell lymphoma, a high-grade malignancy.

Masquerading Clinical Conditions

What makes the clinical examination particularly challenging is that patients present with symptoms that mimic other diseases, Dr. Singh said. For example, patients with vitreoretinal lymphoma often present with nonspecific, benign symptoms such as floaters or blurred vision. As the disease progresses, it can mimic uveitic inflammation and, in many instances, is inappropriately treated with steroids, glaucoma medications, and surgery before the correct diagnosis is made.

“The variety of symptoms and masquerading conditions can lead to a delay of up to two years for an accurate diagnosis for these patients,” Dr. Singh noted.

Clinical clues. Several key clinical features may help ophthalmologists recognize ocular lymphoma. In his research at the Cleveland Clinic, Dr. Singh reported a dominant finding on ophthalmic examination in patients with uveal lymphoma: the presence of yellow-white choroidal infiltrates. He also noted that a majority of patients with uveal lymphoma experienced overlapping involvement with ocular adnexal structures, a finding with treatment implications.² Hans E. Grossniklaus, MD, MBA, at the Emory Eye Center in Atlanta, has noted similar findings.³

Dr. Singh added that some of the clinical scenarios that would warrant a

consideration of a lymphoma diagnosis include ocular inflammation that does not respond to steroids, persistent uveitis in a patient over age 80, persistent conjunctival inflammation, and HLA-A29–negative birdshot retinopathy.

The bottom line, added Dr. Wilson, is that ophthalmologists should keep the possibility of lymphoma in the back of their mind, especially if the patient is not responding to treatment.

Not a Routine Biopsy

Once lymphoma is suspected, the next step is to biopsy the tissue for a definitive diagnosis. Dr. Grossniklaus, one of the few ocular oncologist/ocular pathologists (along with Dr. Wilson) in the United States, has a unique perspective on ocular lymphoma: Not only does he see the patient in the clinical setting but he also interprets the biopsy results.

“Ocular lymphoma poses its own set of complexities for the pathologist,” noted Dr. Grossniklaus. To accurately grade the tumor, he said, “It is important to correlate the histology of the sample with the phenotype and molecular characteristics of the tumor. In addition, a portion of the specimen needs to be fresh and to be submitted properly.”

Pathologists. Dr. Grossniklaus emphasized that ophthalmologists should always talk to the pathologist prior to the biopsy to discuss the optimal way to submit the specimen.

Dr. Wilson added that the pathologist should have expertise in interpreting ocular samples. “Not only are the samples usually smaller,” Dr. Wilson said, “but the fluid is viscous and the tests that pathologists are accustomed to running are based on cells that are in more aqueous solutions.”

Fresh sample. Several different techniques are used, including vitreous, retinal, and subretinal biopsy, and samples should be submitted to the laboratory within one hour of surgery. Immunohistochemistry tests are key to identifying markers for leukocytes, B cells, T cells, and macrophages; and flow cytometry can reveal the proportion of cells that demonstrate these

markers. Polymerase chain reaction (PCR) studies may also be used to obtain a more accurate diagnosis.

Consult. Dr. Grossniklaus added that once an ocular lymphoma diagnosis has been made, a hematologist/oncologist should be consulted to stage it and determine if it is anywhere else in the body. Adnexal and uveal lymphomas tend to occur at visceral sites such as the chest, abdomen, or bone marrow, whereas vitreoretinal lymphoma—being a variant of primary CNS lymphoma—should lead to investigation of the brain, spine, or cerebrospinal fluid for involvement.

A Variety of Treatment Protocols

The nuances associated with diagnosing lymphoma extend to its treatment. “Differentiating the specific subtypes of ocular lymphoma is a challenge, but even with our ability to classify most lymphomas in the eye, it is still a heterogeneous disease,” Dr. Wilson pointed out. “To illustrate, there are at least two different types of large B-cell lymphomas. Consequently, one patient who is treated for vitreoretinal lymphoma may respond differently to a certain treatment protocol than another patient with a similar diagnosis.”

Ocular adnexal. Dr. Grossniklaus said that ocular adnexal lymphomas, which tend to be the low-grade extranodal marginal zone lymphoma (MALT) histologic subtype, usually respond well to external beam radiation. Dry eye is one of the common side effects of radiotherapy. Monoclonal antibody therapy is also being used to treat these lymphomas. Other types of ocular adnexal lymphomas include follicular, mantle cell, and large cell lymphomas. These types of lymphoma are higher grade than the MALT type.

High-grade. When high-grade lymphomas are present in the eye, there is a likelihood that the patient will experience lymphoma in the brain—which calls for the involvement of a neuro-oncologist. In fact, the high-grade lymphomas usually require a multidisciplinary team that includes a neuro-oncologist, ocular oncologist, pathologist, and radiation oncologist.

Throughout the course of treatment, these team members need to maintain communication with each other as well as with the general ophthalmologist.

Dr. Wilson noted that treatment during the last 30 years has evolved. For many years, high-grade ocular and CNS lymphomas were treated with radiation. Although that modality had an immediate effect on the tumor, it was not permanent, and patients tended to develop recurrent disease. Today, chemotherapy can be effective, but many of those drugs do not penetrate the eye well, and they need to be augmented with intravitreal chemotherapy or external beam radiation.

There are several treatment alternatives, including localized external beam radiation therapy, whole brain radiation therapy, systemic chemotherapy, intrathecal chemotherapy, and direct intravitreal chemotherapy.

However, one of the frustrations is that while radiation therapy and chemotherapy, used together, have demonstrated the ability to produce a high response rate, they have not been shown to prevent relapse in CNS lymphoma. Intrathecal or intravitreal methotrexate monotherapy has been used to treat intraocular lymphoma, but this drug, too, has been unable to prevent disease recurrence.

The advent of rituximab, an anti-CD20 monoclonal antibody, either alone or with chemotherapy (both intrathecal and intravitreal) has shown promise. Multicenter studies are needed to determine the efficacy and side effects of the currently available therapeutic options.⁴

An Evolving Field

Dr. Wilson would like to see additional research into the treatment of ocular lymphoma. He noted that a higher number of studies are focused on uveal melanoma (the most common primary ocular cancer) and retinoblastoma. "It is a bit of a failing in our field that we have conducted so many trials on how to treat these two ocular cancers but have conducted so few on ocular lymphoma."

However, he is encouraged by bio-

logics, such as rituximab, which hold the promise of better-targeted therapies against ocular lymphoma. Dr. Wilson predicted that treatment will evolve and improve with the different agents currently in the pipeline, which will ultimately be of great benefit to patients. ■

1 Moslehi R et al. *J Natl Cancer Inst.* 2006; 98(13):936-939.

2 Aronow ME et al. *Ophthalmology.* 2014; 121(1):334-341.

3 Grossniklaus HE et al. *Ophthalmology.* 1998;105(7):1265-1273.

4 Hanson JA et al. *J Cancer Ther Res.* 2013; 2:15. <http://dx.doi.org/10.7243/2049-7962-2-15>.

Hans E. Grossniklaus, MD, MBA, is the F. Phinizy Calhoun Jr. Professor of Ophthalmology, director of the L.F. Montgomery Pathology Laboratory, and director of the Section of Ocular Oncology and Pathology, Emory Eye Center in Atlanta. Financial disclosure: None.

Arun D. Singh, MD, is professor of ophthalmology, and director of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic. Financial disclosure: None.

David J. Wilson, MD, is director of the Casey Eye Institute, and Thiele-Petti Chair in Ophthalmology in the School of Medicine at the Oregon Health & Science University. Financial disclosure: None.

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