Abstract

Ocular adnexal lymphoproliferative disease (OALD) refers to a spectrum of lymphoid disorders affecting the eyelid, conjunctiva, lacrimal gland and orbit. They may be indistinguishable on clinical examination and imaging. Thus, further evaluation is necessary to characterize the lesions and determine whether they are localized or systemic. To highlight the spectrum of disorders, two cases of OALD are presented: one case of benign lymphoid hyperplasia and one case of malignant lymphoma. Diagnosis, management and prognosis of these conditions are discussed. Eyecare providers should be aware of the clinical presentation, diagnostic testing and treatment of the lymphoproliferative disorders as they may present in patients who have no known history of lymphoma and may be readily mistaken for other conditions.

Key Words: lymphoproliferative disorder, lymphoma, benign reactive lymphoid hyperplasia, MALT lymphoma

Background

Ocular adnexal lymphoproliferative disorders (OALD) range from the benign reactive lymphoid hyperplasias (RLHs) to the malignant lymphomas. Both benign and malignant ocular lymphoproliferative disorders typically affect the conjunctiva, orbit and lacrimal gland and are most often unilateral.\textsuperscript{1-5} OALD has a slight female predilection and typically presents between the 5th and 7th decades.\textsuperscript{4,6} Malignant lymphomas and benign lymphoid hyperplasias (LHs) often appear identical on clinical examination and imaging.

We present two cases of OALD that initially appeared similar on clinical examination, but after further evaluation with biopsy, immunohistochemistry and molecular genetics were found to be respectively malignant and benign. Local and whole-body imaging is needed to determine whether lymphoid disease is localized to the orbit or secondary to systemic disease.

This teaching case report is aimed at fourth-year optometry students, residents and current practitioners. Eyecare providers should be aware of the clinical presentation, diagnostic techniques, management options and outcomes for the lymphoproliferative disorders of the ocular adnexa as they may present without prior known history of lymphoma. OALD may be easily mistaken for other conditions, and the eyecare provider may play a significant role in co-management with other disciplines.

Case Descriptions

Case report 1: MALT lymphoma of the palpebral conjunctiva

A 61-year-old black male presented for a routine eye examination with a chief complaint of blurry vision at distance and near. His last eye exam was 35 years ago and the only vision correction he was wearing were over-the-counter readers. He had no history of eye injury or surgery and no personal or family history of ocular disease. His medical history was positive for hypertension, a benign liver mass, hepatitis C, chronic obstructive pulmonary disease, peptic ulcer disease, anemia and past substance abuse. His best-corrected visual acuity was 20/15 for both the right and left eye.

Slit-lamp biomicroscopy revealed a large, red, fleshy and gelatinous conjunctival mass in the left eye that was present in almost the entire inferior fornix, palpebral conjunctiva and encroaching onto the bulbar conjunctiva. The patient was unaware of the mass and was asymptomatic. Lymphoproliferative disease was suspected, and photographs were taken at the initial visit (Figure 1A). All other examination findings were unremarkable.

The patient was referred to the ophthalmology department for evaluation but did not follow up until the next year. At time of presentation with ophthalmology one year later, he was still mostly asymptomatic, although he reported an occasional mild foreign body sensation. The left lower lid now exhibited a slight fullness, and his blink was abnormal with a tendency toward entropion. The pink conjunctival mass involving most of the lower lid and fornix measured approximately 12 mm x 6 mm on the bulbar conjunctiva and 25 mm horizontally on the palpebral conjunctiva. A complete blood count (CBC) with differential was ordered, and the patient was referred to the oculoplastics clinic for biopsy. The CBC revealed a mild elevation of monocytes and basophils but was stable compared with baseline testing over the past 14 years.
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Figure 1. A 61-year-old black male with MALT lymphoma of the inferior palpebral conjunctiva and fornix before (A) and 2 years after (B) treatment with radiotherapy. Click to enlarge.

The patient returned to clinic 2 years later with a complaint of worsening vision in the left eye and glare with nighttime driving. Vision was correctable to 20/20 in the right and left eyes but with glare testing declined to 20/80 in the left eye. Asymmetric cataracts were found, with a denser, milky nuclear sclerotic cataract and a small posterior subcapsular cataract in the left eye. There was no evidence of MALT lymphoma recurrence or systemic involvement (Figure 1B).

Case report 2: lymphoid hyperplasia of the palpebral conjunctiva and fornix

A 68-year-old white male known to the eye clinic presented with a complaint of a “bump” inside his left lower lid for the past 10 days. He noted that initially the lesion felt hard and small, but 4 days prior to the exam it had become flatter and more spread out. The patient had no pain or other associated symptoms. His medical history was positive for hyperlipidemia, hearing loss, erectile dysfunction, chronic kidney disease, migraines and basal cell carcinoma on the left cheek that was removed 1.5 years prior. His last eye exam was 6 months ago at the same clinic and was unremarkable. Best-corrected visual acuity was 20/20 in the right eye and 20/25+2 in the left eye.

Slit-lamp examination revealed a 12-mm horizontal by 5-mm vertical firm, fleshy mass encompassing almost the entire lower palpebral conjunctiva and fornix with no tenderness on palpation. The remainder of the examination was unremarkable. An atypical chalazion was suspected and aggressive hot compresses were initiated. A 1-week follow-up visit was scheduled due to the sudden onset and atypical fleshy appearance of the lesion.

At the 1-week follow-up, the patient reported that the lesion was reduced in size, but examination revealed spreading of the lesion more nasally and into the fornix and inferior bulbar conjunctiva. Best-corrected visual acuity was stable in both eyes. Photographs of the lesion were taken, and the patient was referred to the oculoplastics clinic on the same day for evaluation (Figure 2). The lesion was biopsied, and a pathology evaluation was performed. Immunohistochemistry showed “mixed CD3 and CD20 lymphocytic populations with negative bc12 stain on germinal centers and positive CD10 stain almost exclusively by the follicular center cells.” Immunophenotyping showed a mixture of 36% T cells (CD3+) and 62% B cells (CD19+ and CD20+) and an elevated CD4:CD8 ratio of 6:1. A diagnosis of benign RLH was made.

When the patient returned to the oculoplastics clinic 2 weeks later, the treatment options were discussed with him and he chose observation only at that time. A plan was made to monitor the lesion every 3 months and to consider steroid injections in the future if any growth occurred. However, the patient was lost to follow-up for 8 months. When he returned, the conjunctival lesion was not appreciated. The patient reported that the lesion had resolved on its own approximately 3 weeks after being biopsied.

Education Guidelines

Learning objectives
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1. Understand the spectrum of ocular adnexal lymphoproliferative disease and be familiar with its typical appearance
2. Be aware of differential diagnoses for lymphoproliferative disorders
3. Become familiar with how to manage a patient with suspected ocular adnexal lymphoproliferative disease
4. Become familiar with traditional and emerging immunotherapy treatments for ocular adnexal lymphoproliferative disease

Key concepts
1. Recognize that RLH is clinically indistinguishable from ocular lymphoma
2. Recognize that lymphoproliferative disease is often asymptomatic; however, clinicians should be familiar with common signs and symptoms
3. Become familiar with appropriate workup of suspected ocular lymphomas, including imaging and histology

Discussion points
1. What is the clinical presentation of OALD? What are the differential diagnoses?
2. What additional tests/workup are indicated when OALD is suspected?
3. What is the pathogenesis of lymphoproliferative disease?
4. What is the treatment for OALD?
5. What is the prognosis for OALD?

Literature review
Ocular adnexal lymphoproliferative disease refers to a spectrum of lymphoid disorders affecting the eyelid, conjunctiva, lacrimal gland and orbit. Histopathology classifies the ocular adnexal lymphomas as either benign RLH or malignant lymphoma. Ocular adnexal lymphoma (OAL) is the most common type of OALD and accounts for 68-98% of all lymphoid lesions. OAL is considered primary if it is located solely in the ocular tissues, while secondary lymphoma represents metastasis from another location in the body that is found either subsequently or simultaneously to the systemic lesions. OAL is further categorized into Hodgkin disease and non-Hodgkin lymphoma (NHL).

The majority of OAL is non-Hodgkin B-cell lymphoma, the most common of which is extranodal marginal-zone lymphoma, commonly referred to as MALT lymphoma (46-75%). This type of lymphoma was highlighted in the first case description. Other common types of OAL include follicular lymphoma (4.5-18%), diffuse large-B-cell lymphoma (4.7-16%) and mantle-cell lymphoma (3-9%). Studies have either found no gender predilection, or a slight female majority. The lymphoproliferative disorders are most common in older adults, with a median age of 59-71. Over the past few decades, OALD has been on the rise in Western countries. Studies show annual increases of 3.4-6.5%, mainly due to an increase in ocular adnexal MALT lymphoma.

RLH is a proliferation of lymphoid tissue, usually with a polyclonal mix of small lymphocytes, and is a benign condition. It has a predilection for the orbit and adnexa but only accounts for approximately 7-15% of OALD. RLH is essentially indistinguishable from NHL clinically, and it requires biopsy for diagnosis as demonstrated in the second case description.

Discussion
Teaching instructions: Participants should read each question and consider how they would respond and then read the information provided in the text. Learning objectives are to be assessed by comparing participants’ responses to the information provided.

What is the clinical presentation of ocular adnexal lymphoproliferative disease? What are some differential diagnoses?
Lymphoma is most common in the 5th to 7th decades. LH typically presents 5-10 years earlier. Both of the patients in the cases presented were in their 6th decade. Lymphoproliferative disease has a slight female predominance.
clinical appearances of benign LH and malignant lymphoma are also similar, and they are indistinguishable on clinical examination.\textsuperscript{1,2,8} Lymphoproliferative disease can be asymptomatic and found on routine exam but often presents as a slowly enlarging, painless mass. Common symptoms include proptosis, swelling, diplopia, ptosis, and mild to no pain and inflammation.\textsuperscript{1,2,5,11,17} Vision loss is rare as these lesions mold to the globe and orbit rather than invade the surrounding tissues.\textsuperscript{17,18} The median duration of symptoms before diagnosis is 6-7 months but can range from 1 month to 10 years.\textsuperscript{4,11}

The most common locations involved in lymphoproliferative disorders of the ocular adnexa are the orbit/lacrimal gland (33-46%), conjunctiva (23-42%) and eyelid (10-25%).\textsuperscript{1,8} Conjunctival location usually offers the best prognosis, while eyelid lymphoma is usually secondary to a more aggressive systemic lymphoma,\textsuperscript{3,15} and lacrimal lymphoma is most likely to spread to the lymph nodes.\textsuperscript{19} The majority of OALD is unilateral; only 10-25% is bilateral, which often signifies a poorer prognosis.\textsuperscript{4,12,17}

Orbital and lacrimal gland lesions usually present as a firm or rubbery mass that can lead to proptosis.\textsuperscript{4} Conjunctival lymphoproliferation is often a characteristic “salmon-colored” lesion that is well-circumscribed and either nodular or smooth, as evident in the anterior segment photographs of both patients. It arises from the conjunctival stroma; therefore, the overlying epithelium is unchanged, which is one way of differentiating it from squamous-cell neoplasia.\textsuperscript{14,20}

Differential diagnoses for the clinical presentation of these lesions range from benign entities such as pinguecula, conjunctivitis and pterygium, to malignant ones such as Kaposi sarcoma, ocular surface squamous neoplasia, and amelanotic melanoma.\textsuperscript{4,20} It is important to refer any suspicious or atypical lesions or any non-resolving conjunctivitis for evaluation and biopsy, especially because clinical presentation alone cannot differentiate lymphoma from benign LH.

What additional tests/workup are indicated when ocular adnexal lymphoproliferative disease is suspected?

A thorough workup is needed to diagnose a lesion as lymphoproliferative disease. Careful staging of the disease is needed to determine whether the lesion is localized to the ocular adnexa or if there is concurrent systemic disease. Additional testing should include a physical examination with emphasis on the lymph nodes. Laboratory testing includes a CBC with differential, serum protein electrophoresis, serum lactate dehydrogenase and \( B_2 \)-microglobulin. Tissue biopsy with histological, immunophenotypic and molecular genetic evaluation is necessary, as are orbital and whole-body imaging.\textsuperscript{4,14} In some cases, a bone marrow biopsy may also be necessary if invasion of bone is suspected with more aggressive tumor types.\textsuperscript{5}

While neither patient in the cases presented underwent magnetic resonance imaging (MRI) or computed tomography (CT), MRI and/or CT may aid in making the diagnosis as well as in assessing the exact location and extent of lesions. MRI and CT should be performed with contrast and thin slices through the orbit. On imaging studies, lymphoproliferative lesions typically appear as unifocal, well-circumscribed, homogenous masses that are either isodense or slightly hyperdense to muscle, and they mildly enhance with contrast. The lesions usually mold to solid structures, such as the globe and orbit. Bone destruction is always absent in LH and rare with lymphomas and usually signifies a more aggressive lymphoma, such as diffuse large-B-cell lymphoma.\textsuperscript{4,21}

Additional whole-body imaging is also necessary to look for systemic involvement and to stage the disease. Traditional imaging is performed using CT of the chest, abdomen and pelvis to look for any systemic lesions in lymph nodes, organs or other mucosal sites. Valenzuela and colleagues found that imaging with fluorine 18 deoxyglucose positron emission tomography (FDG PET) upstaged 66% of patients compared with traditional CT scan, which led to a change in the ultimate management of these patients.\textsuperscript{1} Similarly, a study by English et al. demonstrated that FDG PET detected systemic lesions in 31% more cases than CT imaging.\textsuperscript{5} Conversely, FDG PET is less sensitive at detecting orbital lesions compared to CT (27-79% vs. 73-97%, respectively).\textsuperscript{5,21} It has been suggested that combined PET/CT imaging could enhance the detection of the location and extent of disease and ultimately aid in management and final outcome.\textsuperscript{5}

Ocular adnexal lymphoproliferative disorders are clinically and radiologically indistinguishable for the most part, and a full pathological evaluation including histology, immunophenotyping and molecular genetics is needed to confirm the exact type of lymphoid proliferation and to distinguish between benign and malignant disease.\textsuperscript{12} Morphologically, LH is seen as a dense infiltration of small B and T lymphocytes organized into well-defined reactive follicles.\textsuperscript{22} T cells are usually found to be the predominant cell type with immunohistochemistry, which differs from B-cell lymphomas — the majority of OALD. The reactive germinal centers contain “tingible body” macrophages filled with cellular debris, while Dutcher bodies are absent, differentiating LH from marginal-zone lymphomas such as MALT lymphoma.\textsuperscript{14,22} The presence of an infiltrate of small, mostly B-cell lymphocytes surrounding reactive follicles also characterizes MALT lymphoma (distinguishing it by definition from diffuse large-B-cell lymphoma) although a few large cells may be present as well.\textsuperscript{23} Immunophenotyping
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may also aid in differentiating it from other malignant lymphomas. The cells usually express the B-cell antigens CD19, CD20 and CD22 but are negative for CD5, CD10 and CD23, while follicular lymphoma is positive for CD10 and mantle-cell lymphoma is positive for CD5. Flow cytometry in the first case presentation showed CD19, CD20 and CD22 cell markers, which is consistent with a diagnosis of MALT lymphoma, while the second case presentation revealed CD10 cells consistent with a diagnosis of benign RLH.

What is the pathogenesis of lymphoproliferative disease?

Lymphoproliferative disease likely arises initially as an immune response to an antigen as the tissue architecture resembles that of a stimulated lymph node. Both LH and MALT lymphoma occur in locations where lymphocytes are not normally located but converge at the site in response to an antigen. Such stimuli are either from chronic infection, which has been shown with Helicobacter pylori in gastric tumors, or an autoimmune disease, such as Hashimoto’s thyroiditis in thyroid tumors. Infection with Chlamydia psitacci has also been proposed as a precipitating factor in OALD, but studies have shown wide geographic variability, including variability within the same region, and there is no consensus.

In the case of LH, it has been hypothesized that T-cell imbalance drives B-cell proliferation because T cells are often the main cell type in LH and the CD4:CD8 ratio is usually elevated. Also, it has been shown that LH can progress to NHL in cases of helicobacter gastritis, Sjögrens disease and Hashimoto’s disease. It is hypothesized that sustained B-cell proliferation in LH leads to increased mutations and translocation of genes until there is unrestrained proliferation of a monoclonal B-cell population (essentially the definition MALT lymphoma). However, not all lymphoid proliferations progress to lymphoma.

The exact pathogenesis of OALD is still unknown and investigation into the precipitating factors and the genetic mutations involved are ongoing.

What is the treatment for ocular adnexal lymphoproliferative disease?

The management of OALD involves multiple specialties and depends on tumor classification, extent of disease and prognostic indicators. It should only be decided after a rigorous examination, pathological evaluation and staging process.

The traditional treatment for primary OAL is radiotherapy, with a mean total dose of 32 Gy (range 15-46). The patient in our first case report received a total of 36 Gy. The 5-year survival rate can be as high as 95-100% for orbital MALT lymphoma; however, higher doses of radiation or adjuvant treatment are usually needed in higher-grade tumors. Radiotherapy has also been used for LH, but at lower levels, typically 15-25 Gy. Standard treatments in the past have included systemic or injected steroids. Other treatments for OALD include observation only, which may be more appropriate in cases of LH as demonstrated in the second case report, and is not recommended for lymphoma unless the patient is particularly elderly and frail. Surgical excision of encapsulated lesions is another treatment option, although excision has a high rate of recurrence and risk of possible systemic dissemination, especially if no adjuvant radiation or systemic treatment is added.

Adverse effects from radiotherapy can be categorized as acute (either during or within 3 months of treatment) or late (more than 3 months after treatment) and can occur in up to 70% of patients. Acute complications are mostly transient and often resolve spontaneously. Late effects are often chronic and more severe and may include dry eye syndrome, loss of eyelashes, cataracts, retinopathy and optic neuropathy. Radiation retinopathy typically occurs with doses of 45-60 Gy but may occur with doses as low as 18 Gy when there is underlying vascular compromise such as diabetes.

For secondary orbital lymphoma with systemic involvement, systemic chemotherapy is typically the first-line treatment. Treatment of low-grade lymphoma often involves a single drug such as chlorambucil, while a multiagent regimen such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is used for more aggressive histological types. Combination treatment with both local radiation and systemic chemotherapy, termed chemoradiotherapy, may offer more favorable outcomes in patients with more advanced disease, but there have been no large trials confirming the optimal protocols. Complications from systemic chemotherapy include nausea, anemia and neutropenia, which may be life-threatening.

In a small, retrospective study by Paik et al. in 2012, researchers compared 24 patients with non-conjunctival ocular adnexal MALT lymphoma. Nine patients received chemotherapy only, eight received radiotherapy only (30-40 Gy), and seven received adjuvant radiotherapy (30-36 Gy) after chemotherapy provided insufficient response. They scored the ophthalmologic outcomes based on six main criteria that they deemed most common and important: decreased vision, dry
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eye, cataract, intractable intraocular pressure, retinopathy and blepharitis. They found that visual outcomes, as well as dry eye and blepharitis, were more common and serious in patients who received either radiotherapy alone or chemoradiotherapy vs. chemotherapy alone. Overall, patients treated solely with chemotherapy had better ocular and visual outcomes, and it should be considered as an alternative to radiotherapy.\cite{29} Other case reports have also shown superior ophthalmologic outcomes with chemotherapy for primary disease. Dimitrakopoulos and colleagues stated that “although radiotherapy is preferable for localized lymphoproliferative lesions, chemotheraphy also should be considered as an effective treatment that preserves the integrity and function of the ocular adnexa.”\cite{20}

Immunotherapy, most notably using the monoclonal antibody rituximab, is an emerging treatment for OALD. Rituximab targets the CD20 cell-surface receptor, which is found on all normal B cells and the majority of malignant B cells, leading to apoptosis. Single-agent systemic treatment with rituximab for patients who have received no prior treatment shows overall response rates of 50-100%, with either partial or complete remission.\cite{4,25} Unfortunately short-term recurrence is common, although a small case series by Annibali et al. showed improved results with maintenance therapy.\cite{10,26} Therefore, despite its better toxicity profile, rituximab is usually not used as monotherapy but rather is often added to chemotherapy, which may reduce the risk of failure.\cite{12} Rituximab is also used to treat LH when steroids or radiotherapy has failed. Cases of complete remission have been reported after use of rituximab as a first-line treatment.\cite{10,14}

Radioimmunotherapy is another new treatment option that adds a radioactive isotope to an anti-CD20 antibody. The radiation is emitted over an area greater than 100 cell diameters. Nearby tumor cells that are CD20-negative are also affected, a process called the ‘crossfire effect’.\cite{10,14} Response rates are as high as 90%, but studies of long-term outcomes are still needed.\cite{10}

What is the prognosis for ocular adnexal lymphoproliferative disease?

The prognosis of OALD ultimately depends on type of lesion, extent of disease and treatment modality. Studies have shown that 31-44% of patients with OAL also have systemic lymphoma at the time of diagnosis. Systemic involvement is more likely in patients with bilateral disease and in patients diagnosed with high-grade tumor types.\cite{11-20,20} Based on the Kaplan-Meier survival analysis, studies have shown that systemic disease is likely to occur in 7-8% of patients at 1 year, 15-17% at 5 years, and 28-33% at 10 years with a greater risk in patients with bilateral involvement.\cite{11,20} A study by McKelvie et al. found that lymphoma-related deaths occurred in 18% of patients with OAL over 5 years of follow-up, but only in 2% of patients with MALT.\cite{15} Mortality was higher for follicular lymphoma (33%) and diffuse large-cell lymphoma (38%), but was 100% for the more aggressive types, such as mantel-cell lymphoma, peripheral T-cell lymphoma and natural killer-cell lymphoma.\cite{12}

In general, the risk of systemic involvement and death is greater in the more aggressive histological types of lymphoma and in patients with a more advanced stage of disease. MALT lymphoma usually has an indolent course with low likelihood of systemic involvement and lymphoma-related death regardless of the treatment modality selected. However, due to the risk of metastasis and possible transformation to a more aggressive lymphoma, all patients with OAL should be followed every 6 months for at least 5 years, including physical exam, laboratory tests and imaging.\cite{11}

Conclusion

We presented two cases of OALD that initially appeared similar on clinical examination, but after further evaluation with biopsy, immunohistochemistry, and molecular genetics were found to be respectively malignant and benign.

Advances in diagnostic techniques have allowed for better differentiation and classification of OALD. However, benign and malignant OALD are still indistinguishable on clinical examination and further testing is required. New MRI protocols may begin to be able to differentiate between benign LH and malignant lymphoma, but a histomorphological and immunohistochemical evaluation is still needed to confirm the exact histological type, which ultimately guides management. Whole-body imaging is needed to discover any systemic involvement, and combined PET/CT might prove to be the most sensitive way to simultaneously detect both orbital and systemic disease.

In addition to the traditional treatments of radiotherapy and chemotherapy for primary and systemic OALD, respectively, emerging treatments might offer better outcomes with less adverse effects. Immunotherapy with rituximab and radioimmunotherapy show promising results, especially when added as an adjunct to traditional treatments. New insights into the underlying etiology of lymphoproliferative disorders might also shed light on new treatments such as antibiotics, but there is no conclusive evidence at this time.

Benign lymphoid hyperplasia and MALT lymphoma of the ocular adnexa have an indolent course, and systemic involvement...
and tumor-related deaths are rare given their favorable response to treatment. However, progression and metastasis are risks, and patients should be monitored closely for at least 5 years, even after remission has occurred.

References

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