

Ocular Adnexal Lymphoma: Classification, Clinical Disease, and Molecular Biology

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Although ocular adnexal lymphomas (OAL) constitute a small fraction of all systemic lymphomas, they are among the most common ocular adnexal tumors in most series and represent a group of lesions encountered by many general ophthalmologists and ocular oncologists in practice. Despite the importance of lymphoproliferative disease in ocular oncology, understanding of these conditions has been hampered by imprecision in diagnosis, by a classification that, in addition to being confusing and changeable, did not include OAL until this decade, and by the fact that most patients undergo most of their evaluation and therapy by oncologists as opposed to ophthalmologists.

The past decade has been a time of intense progress in the understanding of lymphoma. Great strides in understanding the molecular biology and molecular genetics of lymphocytes have led to better understanding of lymphocyte biology. A new classification has decimated the confusion previously seen with lymphoproliferative disease, allowing a better distinction of benign from malignant disease and identifying more meaningful groups related to tumor prognosis. Novel mechanisms of tumor pathogenesis have related lymphoma to infection, leading to new approaches to diagnosis and treatment.

Although a broad spectrum of lymphomas can affect the eye and orbital tissues, this article is limited to those that affect the orbit, lids, lacrimal gland, and conjunctiva. Primary intraocular large B-cell lymphoma,

a subset of primary central nervous system lymphoma, is discussed elsewhere in this issue.

Epidemiologic aspects of ocular adnexal lymphoma

Lymphoma has recently been estimated to be the fifth most common malignancy. The incidence of non-Hodgkin's lymphoma is estimated to be rising 4% per year and to have doubled in the last two decades. [1] About one half of these cases are thought to be due to changes in classification as well as an increase in AIDS and better reporting of tumor cases [2]. The remainder are thought to be due to an increase in chronic antigen stimulation, chronic immunosuppression, and as yet speculated environmental factors [3–6]. Although AIDS has increased the diversity of lymphoma presentations, the larger portion of the increase is thought to be an increase in diffuse large B-cell lymphoma (DLBCL) in the elderly.

Ocular adnexal lymphoma is cited to constitute approximately 6% to 8% of orbital tumors [7–9]. An incidence study in an ophthalmic pathology laboratory covering 55 years revealed 10% to 15% adnexal lymphoproliferative lesions but did not analyze chronologic changes in incidence [10]. A frequently cited 30-year-old study of lymphoma incidence data showed that OAL represented 6% of extranodal lymphoma cases [11]; however, improvements in classification have rendered that information obsolete. Most recent studies show a higher percentage of OAL, because many cases previously difficult to

This work was supported in part by Research to Prevent Blindness (unrestricted grant), NIH P30 11373, Ohio Lions Fund.

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Table 1
Distribution of ocular adnexal lymphoproliferative lesions

| Study | Number of patients | OAL (%) | RLH (%) | Other (%) | Primary OAL (%) | Secondary OAL (%) |
|-----------------------|--------------------|---------|---------|-----------|-----------------|-------------------|
| Jakobiec | 117 | 70 | 27 | 3 | — | — |
| Coupland | 112 | 88 | 11 | — | — | — |
| Sharara ^a | 43 | 37 | 10 | 51 | — | — |
| Mannami | 76 | 68 | 29 | 3 | 83 | 17 |
| Nakata | 77 | 57 | — | — | 57 | — |
| McKelvie ^a | 73 | 92 | 8 | — | — | — |
| Cho | 68 | NA | — | — | 85 | 15 |
| Johnson ^a | 77 | — | — | — | — | — |
| White ^a | 48 | 90 | 4 | 6 | — | — |

Abbreviations: NA, not applicable; RLH, reactive lymphoid hyperplasia.

^a Primary/secondary not specified.

classify on morphologic grounds alone are now clearly identifiable as lymphoma using contemporary classification (Table 1) [12–21]. Although a variety of lymphoma types constitutes OAL, most are non-Hodgkin's B-cell type, with less than 1% to 3% T-cell types in all series. Burkitt's and Hodgkin's lymphomas in the ocular adnexae are rare except in endemic regions.

Ocular adnexal lymphoma is considered primary if it involves the ocular adnexa alone and secondary if it is accompanied by a lymphoma of identical type at another site. The extent of OAL is defined as solitary if it involves one or both orbits only, extension if it involves contiguous sites such as the sinuses, and systemic if remote sites are involved.

The frequency of involvement of periocular sites has been reported as follows: conjunctiva, 20% to 33%; orbit, 46% to 74%; and eyelid, 5% to 20% [12,13,19]. These numbers are somewhat variable and may not reflect as clear a distinction as implied, because separation between these immediately proximate structures can be difficult to make, and few studies describe combinations of sites of involvement, a phenomenon that the author has observed. Estimates of multisite involvement range from 10% to 20% [22,23]. Bilaterality is reported in 10% to 20% of cases.

Pathogenesis of ocular adnexal lymphoma

One recent major advance has been the discovery of the relationship between microorganism infection causing chronic antigen stimulation and lymphoma. This mechanism has been most profound with the gastric mucosa-associated lymphoid tissue (MALT) lymphomas, which are thought to be related to *Helicobacter pylori* infection in more than 90% of cases [24]. The theory suggests that chronic antigen

stimulation results in a lymphoproliferative response that ultimately develops into lymphoma. Treatment of the antigenic instigation and gastritis with 1 week of triple antibiotic therapy seems to result in complete resolution of stage I lymphoma in more than 60% of cases [25].

This finding has been identified in a small series of OAL using DNA microcapture, polymerase chain reaction (PCR), and Southern blot techniques [26]. A recent pioneering study demonstrated that 32 of 40 patients with OAL contained DNA of *Chlamydia psittaci* in the tumor specimen compared with 3 of 26 detections in reactive lesions and no such DNA in normal biopsies [27]. The finding seemed specific to *C psittaci* but not other chlamydial species. In addition, 9 of 21 (43%) patients carried *C psittaci* DNA in their peripheral blood cells compared with no detection in controls.

This discovery of the relationship between OAL and chronic infection, although preliminary, may be the missing link in explaining how the orbit, which has no known lymphoid system, and the conjunctiva and lid, which, although having lymphatic channels, are typically devoid of developed lymphoid tissue, can serve as a common site for the development of lymphoma. Further studies are needed to determine the frequency of this occurrence and whether other organisms can be associated with OAL development.

Relationship of B-lymphocyte development and lymphoma

Lymphomas are believed to arise from specific developmental stages of lymphocytes. The behavior of the tumors reflects the behavior of the lymphocytes, with more active cells in aggressive tumors and less active cells in indolent tumor. The many stages of B-cell maturation can be grouped into three phases of

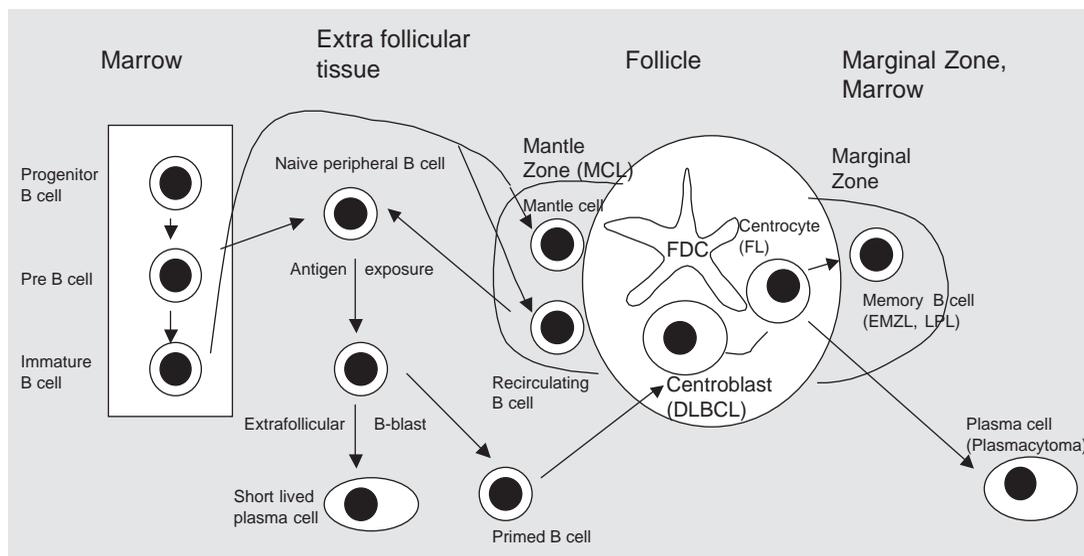


Fig. 1. Simplified model of B-cell development. Tumors arising from a given cell line are shown in parentheses. DLBCL, diffuse large B-cell lymphoma; EMZL, extranodal marginal cell lymphoma; FDC, follicular dendritic cell; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma.

development that differ with respect to their relationship to lymphoma development: (1) early stem cells and pro-B cells, which are foreign antigen independent; (2) fully differentiated plasma cells; and (3) a number of intermediate stages during which foreign antigen exposure is related to the development of lymphoma. These stages extend from a pre-B cell to the memory B cell. A simplified summary of B-cell development is shown in Fig. 1. Mature naïve B cells give rise to mantle cell lymphoma. Follicular lymphoma and DLBCL are thought to arise from cells in the germinal center. Extranodal marginal zone lymphoma (EMZL) and lymphoplasmacytic lymphoma (LPL) arise from memory B cells.

Techniques for classification of ocular adnexal lymphoma

The classification of lymphoproliferative disorders has been one of the more challenging prob-

lems in diagnostic pathology. The pleomorphic and highly dynamic nature of lymphocytes when compared with most other cell lineages has resulted in classifications that, despite extreme efforts, still have limitations. Answers to the two main questions, that is, deciding whether a lesion is benign, transitional, or malignant, and identifying meaningful groupings of tumors, have been imprecise.

With the development of immunohistochemical analysis, clonality can sometimes be identified, helping to answer the first question but leaving the second relatively unanswered. More specific immunophenotyping of lymphocytes via the CD molecules they express has increased understanding of the nature of the cells in an LPL. Flow cytometry, permitting quantitative single cell immunophenotypic analysis (IPA), allows for relatively rapid quantitative analysis of lymphocyte populations, enabling a more comprehensive understanding of the composition of these lesions. IPA relevant to the diagnosis of OAL is presented in Table 2. Molecular genetic analysis

Table 2
Immunophenotype analysis of ocular adnexal lymphoproliferative lesions

| Type | CD3 | CD5 | CD10 | CD20 | CD23 | CD43 | CD79 | Bcl-2 | Bcl-6 | Cyclin D1 |
|-------------------------------|-----|------|--------------|------|------|------|------|-------|-------|-----------|
| EMZL | - | - | - | + | - | + | + | - | - | - |
| Follicular | - | - | + | + | ± | - | | + | + | - |
| Mantle cell | - | + | - | + | | | | - | | + |
| Lymphoplasmacytic | - | + | - | + | + | | | | | |
| Diffuse large B-cell lymphoma | - | -(+) | +(25% - 50%) | + | | | + | | | |

allows for the identification of immunoglobulin heavy chain gene rearrangements, signifying clonality, which can be detected in very small specimens via the use of PCR amplification of DNA. Chromosomal analysis using whole chromosome techniques, PCR-aided blot techniques, and fluorescent *in situ* hybridization (FISH) analysis have demonstrated the presence of characteristic nonrandom chromosomal alterations, such as translocations, which have helped to characterize and advance understanding of the molecular pathogenesis of these lesions. Expanded understanding of the molecular biology of the lymphocyte has allowed for better correlation with genetic alterations and morphology and, in some cases, has permitted the use of immunohistochemistry to identify specific gene products, bypassing the need for direct genetic analysis in some cases.

Classification of ocular adnexal lymphoma

Although the Revised European American Lymphoma (REAL) classification, the first accepted classification formally including extranodal disease such as OAL, was proposed in 1994, series of OAL using this classification have been reported only recently [28]. The World Health Organization (WHO) classification (2001) represents a modification and validation of the REAL classification and should be applied to any current or future study [29]. To understand the power, flexibility, and importance of the current classification, a brief historical description is in order.

The Rappaport classification was morphologically based on growth pattern (nodular/diffuse), cell type (lymphocytic/histiocytic), and the degree of differentiation [30]. It was followed by the development of several classifications that were essentially morphologic and based on cell size (small or large), nuclear characteristics (cleaved/noncleaved), and the shape and pattern of growth (follicular or diffuse) [31,32]. The National Institutes of Health (NIH) sponsored Working Formulation (1982) was developed to unify these disparate approaches and combined clinical and morphologic features with early immunologic data, separating non-Hodgkin's lymphomas into low, intermediate, and high grades. Within each grade, subtypes, based primarily on morphology, were identified, but this grouping was not intended to be an independent classification [33]. The understanding of lymphocyte biology rapidly expanded based on molecular biologic and molecular genetic data identifying cell surface markers. This more precise characterization of lymphocytes demonstrated that

there were more subtypes than previously appreciated. In addition, the position of a cell within a lymph node and whether it had interacted with an antigen or antigen-presenting cell could be detected.

The International Lymphoma Study Group sought to develop a comprehensive, accurate, and practical classification, which would represent real disease entities as opposed to arbitrary classifications based on histologic, organizational, or prognostic characteristics. By using the collaborative effort of a large group of international experts instead of the experience of an individual or center, and by using published data instead of speculative or hypothetical conceptualizations of tumors, the REAL classification combined histologic, immunophenotypic, molecular genetic, and clinical data to allow better distinction of specific entities. It also incorporated the International Prognostic Index, a collection of clinical features that correlate well with clinical behavior [34].

The WHO classification was the result of further multidisciplinary work to validate and revise the REAL classification, with minor additions and deletions and expansion to include more types of lymphoid malignancies. The WHO classification included all cases and increased accuracy and reproducibility. One example of the importance of the WHO classification of OAL is that, in some studies in which WHO criteria were applied retrospectively, more than 25% of lesions ultimately classified as EMZL had originally been classified as benign reactive lymphoid hyperplasia (RLH) [35]. So-called "MALT lymphomas" are classified as EMZL in the WHO classification. EMZL/MALT can occur without juxtaposed mucosa. Such lymphomas have been most commonly identified in the thyroid, lung, salivary gland, and lacrimal gland [36]. Less common sites include the orbit, conjunctiva, skin, breast, bladder, and kidney [37]. These tumors are thought to have a clinically indolent course.

Although the classification of lymphoma is extensive, OAL exhibits a limited spectrum, with the vast majority of tumors being B cell in nature and almost all non-Hodgkin's types. OAL falls into one of five or six types. Data regarding the distribution of these more common types are listed in Table 3 [37–40]. Most (50% to 90%) OALs are classified as EMZL type.

Molecular genetics of ocular adnexal lymphoma

A variety of translocations have been identified in several forms of non-Hodgkin's lymphoma. The most

Table 3
Distribution of types of ocular adnexal lymphoproliferative lesions

| Series | Year | OAL | | | | | | | |
|----------|------|----------------|----------|----------------|-----------------|-----------------------|--------------------------|-------------------|--------|
| | | patients (no.) | EMZL (%) | Follicular (%) | Mantle zone (%) | Lymphoplasmacytic (%) | Diffuse large B cell (%) | Plasma cytoma (%) | T cell |
| Coupland | 2003 | 230 | 59 | 12 | 3 | 4 | 13 | 4 | 3 |
| Fung | 2003 | 98 | 57 | 18 | 4 | — | 7 | — | — |
| McKelvie | 2001 | 70 | 63 | 17 | 3 | — | 11 | — | 1 |
| Shields | 2001 | 117 | Not done | — | — | — | — | — | — |
| Mannami | 2001 | 43 | 86 | — | 2 | — | 12 | — | — |
| Bhatia | 2001 | 47 | 17 | 53 | — | — | 26 | — | — |
| Sharara | 2003 | 17 | 47 | 12 | 18 | 6 | 18 | — | — |
| Jenkins | 2000 | — | 54 | 11 | 2 | 24 | 8 | — | <1 |
| Nakata | 1999 | 44(57) | 77 | — | 4 | 2 | 14 | — | — |
| White | 1995 | 43 | Not done | — | — | — | — | — | — |
| Cho | 2003 | 57 | 98 | — | 2 | — | — | — | — |
| Range | | | 17–98 | 11–53 | 2–18 | 4–24 | 7–26 | 4 | 1 |

common of these are presented in Table 4 [41,42]. These molecular genetic abnormalities can be detected directly through the detection of altered nucleic acid material or indirectly through the detection of abnormally expressed proteins encoded by the altered genetic material.

In marginal zone lymphomas (MALT type), genetic alterations include t(11;18)(q21;q21), t(14;18)(q32;q21), t(1;14)(p22;q32), and t(1;2)(p22;p12) [43]. The first two alterations have been identified in one of three and one of five of systemic EMZL lymphomas, respectively. The t(11;18) translocation seems to be specific for the MALT subtype of marginal zone lymphomas. There are limited and discrepant data regarding the identification of this gene alteration in OAL.

In mantle cell lymphoma, t(11;14)(q32;q32) can be detected using FISH analysis in as many as 95% of tumors and by cytogenetic analysis in 79% to 80% [44]. The translocation results in overexpression of cyclin D1, a reliable marker for mantle cell lymphoma within the family of B-cell non-Hodgkin's lymphoma used for following the disease course.

In follicular lymphoma, the t(14;18) translocation can result in overexpression of Bcl-2, a protein not seen in normal germinal centers but present in follicular lymphoma [45]. Identifying overexpression of Bcl-2 can help distinguish between benign and malignant follicular processes.

Diagnosis of ocular adnexal lymphoma

Clinical and imaging data cannot be used to make the diagnosis of OAL with certainty. Diagnosis is made based on a combination of histopathologic, immunophenotypic, and molecular genetic information. Diagnostically, three questions are asked: (1) Is the lesion malignant (OAL), transitional (atypical RLH), or benign (RLH)? (2) What specific type of OAL is present? (3) Can specific prognostic features be identified?

Routine histologic analysis can often answer the question of the degree of malignancy. Nevertheless, because the WHO classification is dependent on immunophenotype and molecular genetic data, lym-

Table 4
Genetic alterations in types of non-Hodgkin's lymphoma presenting as ocular adnexal lymphoproliferative lesions

| Type | Genetic change | Mechanism | Frequency | Proto-oncogene |
|-------------------------------|-------------------|-------------------------|-----------|----------------------------------|
| EMZL | t(11;18)(q21;q21) | Fusion | 50% | <i>API2/MLT</i> |
| | | Transcript deregulation | Rare | <i>Bcl-10</i> |
| Follicular | t(14;18)(q32;q21) | Transcript deregulation | 80%–90% | <i>Bcl-2</i> |
| Mantle cell | t(11;14) | Transcript deregulation | 70% | <i>Bcl-1</i> (encodes cyclin D1) |
| Lymphoplasmacytic | T(9;14)(p13;q32) | Transcript deregulation | 50% | <i>PAX-5</i> |
| Diffuse large B-cell Lymphoma | Der(3)(q27) | Transcript deregulation | | <i>Bcl-6</i> |

phoproliferative lesions should undergo IPA for B-cell and T-cell markers, heavy and light chain restriction, CD5, CD10, CD23, cyclin D1, and bcl-2. When possible based on the amount of available tissue, flow cytometry should be performed because of its quantitative nature.

Immunophenotypic analysis can answer several general questions, such as cell type distribution and clonality vis-a-vis restriction of light chain to κ or λ expression. The histologically similar mantle cell and marginal cell tumors can usually be distinguished owing to the differential expression of CD5.

Molecular genetic analysis for gene rearrangements of the IgG heavy chain can identify clonality at a much more sensitive level but can provide false-positive data (especially in PCR-amplified studies) based on sampling problems. One issue regarding prognosis involves the meaning of clonality. It has been questioned whether lesions demonstrating evidence of clonal proliferation but that are otherwise thought to represent reactive and not neoplastic processes are, in fact, early or precursor lymphomas, and whether techniques, especially those that rely on intense amplification of small samples of DNA, may artifactuously create the illusion of clonality.

When the classification of OAL was based on nuclear features, emphasis was placed on fixing some of the specimen in B5 fixative and maintaining some in an unfixed state. Although fresh tissue is still considered superior for IPA and molecular genetic analysis, improvements in antigen retrieval techniques allow for tissue fixation in 4% neutral buffered formalin. Flow cytometric studies still require unfixed tissue. Prebiopsy consultation with the pathologist is still advised for optimal specimen analysis.

Clinical evaluation and staging of the patient with ocular adnexal lymphoma

Management of OAL is optimally an integrated multidisciplinary endeavor requiring a comprehensive staging evaluation. The importance of comprehensive staging was demonstrated by a study showing a steady progressive increase in the disease stage as the extent of evaluation increased [46]. A thorough physical examination by a physician familiar with lymphoma is optimal. The use of ancillary staging studies has evolved with the development of new imaging modalities. Imaging and fine-needle biopsy have replaced laparotomy, although some question the ability of fine-needle aspiration biopsy to obtain diagnostically representative specimens. A

recent case-based survey of radiation therapists with expertise in managing lymphoma recommended the following studies: complete blood count, hepatic enzyme levels, lactate dehydrogenase, CT of the abdomen and pelvis, chest radiography, CT of the chest, and bilateral bone marrow aspirates more than half the time [47]. In one study, a quarter of patients with stage IV disease were upgraded from stage I based on bone marrow biopsy, underscoring its importance.

If conjunctival or eyelid OAL is identified clinically, MRI or CT of the orbit is indicated for staging. In one study, 50% of patients with apparently solitary conjunctival disease had orbital disease revealed by neuroimaging [22]. If there is palpable cervical adenopathy, imaging of this region is performed as well.

The role of positron-emission tomography (PET) scanning in lymphoma staging and more particularly in staging of OAL is not established. PET has greater sensitivity in detecting abnormalities than does CT or MRI, but the significance of minimal lesions is not known.

Natural history, prognosis, and outcome of ocular adnexal lymphoma

Three outcomes are relevant to OAL. The first is the status of the local orbital disease, recurrence if it is treated, or progression if it is not. The second is the extension of lymphoma regionally or systemically, and the third is death from lymphoma. Factors that are prognostic candidates include the disease stage at presentation, the type of lymphoma, the site of disease, increased expression (>10% of tumor cells) of pRB, p53, and Bcl-6, high tumor growth fractions as indicated by MIB-1, and the increased age of patients [21]. Data regarding these parameters are shown in Table 5 but can be difficult to compare because of different methods and selective analyses used in various studies.

The site of presentation of OAL has been associated with prognosis. A prospective study identified the pattern of site-related prognosis as measured by systemic involvement, with 20% of conjunctival, 35% of orbital, and 67% of eyelid OALs showing extraorbital lymphoma [12]. A later study showed an incidence of 38%, 54%, and 100% of disease, respectively. Other studies have shown little difference between the sites [38]. The data regarding disease progression must be scrutinized well, because some series combine primary and secondary OAL,

Table 5

Frequency of primary and systemic lymphoma, posttreatment extension, and lymphoma-related death in ocular adnexal lymphoproliferative lesions

| Study | Number of patients | Solitary (%) | Extraorbital at diagnosis (%) | Extraorbital posttreatment (%) | Tumor-free rate at 5 yr/10 yr | Lymphoma death (%) |
|----------|--------------------|--------------|-------------------------------|--------------------------------|-------------------------------|--------------------|
| Jenkins | 192 | 64 | 36 | 53 | — | 26 |
| Auw | 46 | 78 | 22 | 39 | — | 26 |
| Cahill | 20 | 70 | 30 | — | — | — |
| Mannami | 42 | — | — | — | — | — |
| Fung | 84 | 63 | 25 | — | 75/45 | 0 |
| Coupland | 230 | — | — | — | — | 25 |

obscuring the actual degree of OAL spread, and treatment regimens may vary considerably.

The type of lymphoma seems to have prognostic value in most studies. Mortality as a function of lymphoma type is shown in Table 6. Among the common OAL tumor types, EMZL, follicular lymphoma, and LPL are considered low grade or indolent, whereas DLBCL and mantle cell lymphoma are considered high grade. Data reported by Jenkins suggested that OAL of the EMZL type had an indolent course in comparison with more aggressive lymphoma but not better than that of other low-grade lymphomas, because, overall, half of patients showed systemic spread after treatment [40]. The mean time to relapse was over 5 years, suggesting that longer follow-up than typically recommended is needed. Relapse and death from lymphoma can occur for many years at rates similar to that reported for other low-grade lymphomas. There is no evidence that patients with low-grade OAL including EMZL should be considered cured [36]. This observation is further supported by the data of Fung who found a 45% relapse-free rate for OAL at 10 years in contrast to rates of 90% or greater for gastric EMZL [42].

Management of ocular adnexal lymphoma

The selection of treatment for OAL is dependent on the specific tumor type and its staging. Con-

troversy exists as to whether OAL is curable. Those who believe so pursue more aggressive but potentially toxic therapies, whereas those who believe it is not curable may treat indolent disease only as it becomes symptomatic or transforms to high-grade lymphoma. Other clinicians will treat the patient based on an attempt to prevent transformation to a high-grade lymphoma. In some cases, observation without intervention is selected.

Surgery

Although surgery can be used for certain cases of lymphoma and has been particularly advised for stage I MALT systemic lymphoma in some sites, this modality is typically reserved for selected cases of OAL. This approach is due in part to the close juxtaposition of important structures combined with the often diffuse or multicentric nature of OAL. Excision may be most appropriate for localized lesions of the conjunctiva and orbit [21,23].

Radiation

Radiation has been the most frequently used modality for treating OAL, because many patients present with localized disease. Interpretation of studies of radiation treatment of OAL has been confounded by the small patient number, the use of early classifications, or the grouping of cases by tumor “grade.”

Table 6

Mortality with ocular adnexal lymphoproliferative lesions

| Series | EMZL (%) | DLBCL (%) | FCL (%) | MCL (%) | LPL (%) |
|----------|----------|-----------|---------|---------|---------|
| McKelvie | 2 | 38 | 33 | 100 | 100 |
| Coupland | 13 | 42 | 37 | 38 | 44 |
| Fung | 20 | 25 | 20 | — | — |
| Jenkins | 9 | 30 | 21 | NA | 14 |
| Nakata | 0 | 75 | — | 75 | — |

Abbreviations: FCL, follicular lymphoma; MCL, mantle cell lymphoma; NA, not analyzed separately.

Electron or photon irradiation can be used depending on the site and extent of disease. A wide variation of doses has been recommended, ranging from lows of 15–20 Gy up to 40 Gy. Typical doses are 28 to 36 Gy for low-grade OAL and 30 to 40 Gy for high-grade disease. Controversy exists about the use of lens shielding to reduce cataractogenesis. Some studies show no effect on local recurrence, whereas in others, all recurrences have occurred in patients whose lenses were shielded [38–40,48,49]. Complications have been noted at a higher rate (up to 50%) in studies with evidence of close ophthalmic follow-up.

One study has used the WHO classification and assessed the dose-response of radiation. The local 5-year control rate of EMZL-MALT was 81% with doses less than 36 Gy but 100% with doses greater than 30 Gy [38]. There seems to be differential susceptibility of various types of OAL, with follicular lymphoma responding to higher and lower doses at a 100% rate. Nevertheless, it is not clear that successful local control as reported by many studies affects the ultimate outcome of disease. Local control even with stage IV-EA disease was good even though survival was less. The data of Jenkins et al cited previously as well as that of others suggest that longer follow-up is needed to assess overall treatment effect [40]. Recurrences of low-grade types are often treatable with local modalities.

The use of local brachytherapy with strontium has been reported but seems to be associated with significant numbers of local recurrences as well as ocular toxicity [50].

Chemotherapy

A comprehensive discussion of chemotherapy for lymphoma is beyond the scope of this article. With solitary OAL, systemic chemotherapy is not believed to be indicated, except with DLBCL. Chemotherapy for OAL when it is part of stage II or greater disease has included the use of standard regimens for systemic lymphoma, including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), chlorambucil, as well as many other combinations of agents.

Cryotherapy

Cryotherapy has been used infrequently for OAL, with varying success. Typically, it is used in patients with conjunctival lymphoma to reduce tumor bulk [23].

Immunotherapy

Interferon treatment

Interferon (IFN) has been used in the treatment of systemic lymphoma for over two decades. There are scattered reports of the local use of IFN- α for OAL [51]. Five patients with solitary conjunctival disease (four with stage IE and one with stage IIA disease in remission after chemotherapy) were treated with intralesional IFN- α , 1,500,000 IU three times weekly for 4 weeks followed by 1,000,000 IU three times weekly for 4 weeks and then 1,000,000 IU every 2 weeks four times. An initial complete response was reported for all patients, and 80% were disease free with short follow-up. The patient with stage IIA disease died of systemic lymphoma 1 year later. Side effects included a flulike syndrome. Long-term studies with more patients evaluating local and systemic recurrences are needed before interferon can become an established therapy for OAL.

Antilymphocyte antibody treatment

Antilymphocyte antibodies represent the newest form of lymphoma treatment. Using antibodies to CD20 (rituximab), destruction of B cells can take place based on the induction of apoptosis, complement-mediated cytotoxicity, and antibody-dependent, cell-mediated cytotoxicity [52,53]. These agents have been introduced clinically and have been used most often with other modalities systemically. One small series regarding rituximab use in OAL has been reported [54]; however, only one of eight patients had primary OAL, and only two of eight patients received rituximab alone. The patient with solitary OAL also received radiation, cyclophosphamide, vincristine, and prednisone. The two patients receiving antibody alone showed only partial responses or recurrence. The study did not separate the effects of the other treatments from the effect of the rituximab despite claiming “good effect of the rituximab.” This author has managed cases of primary OAL with systemic involvement in which rituximab in combined therapy led to partial regression, whereas in other patients no effect was seen.

Antimicrobial treatment

Perhaps the most exciting development in the field of lymphoma management is the finding that, in microbial-associated MALT lymphomas, antimicrobial treatment can lead to remission. This effect is best described for gastric lymphoma with antimicrobial treatment directed against *H pylori*.

The previously discussed data associating OAL with *C psittaci* also described the first patients with

OAL treated with antibiotic against the inciting agent [27]. Seven patients with evidence of *C psittaci* in the tumor and peripheral blood mononuclear cells were treated with doxycycline, 100 mg three times daily, for 3 weeks. All of the treated patients showed eradication of chlamydial DNA from peripheral blood mononuclear cells. Two of four patients with measurable OAL demonstrated objective responses. The author and his colleagues have recently treated a patient with RLH affecting the orbit and multiple lymph nodes with doxycycline. A rapid subjective and objective response was observed. Further studies are needed to verify this infectious association and those with other possible inciting pathogens.

Blood cell progenitor ablation and reconstitution. Another newer approach to the management of systemic lymphoma involves destruction of the hematologic source of the tumor followed by reconstitution, typically with a hematologic stem cell progenitor transplant [55]. Although this modality is not being used for OAL, ophthalmologists should be aware of this treatment and the numerous ocular problems associated with such transplants, including graft versus host disease, sicca syndrome, and medication side effects, which can require intense and specialized care.

Summary

The study of ocular adnexal lymphoproliferative disease has benefited greatly from the incorporation of new data in the realms of molecular biology and genetics. Application of the WHO lymphoma classification based on better understanding of lymphocyte biology has increased the accuracy of diagnosis of OAL by better differentiating it from RLH and separating it into cohesive prognostic groups. Most OAL is EMZL (MALT type), and the resolution of previously uncharacterized cases has increased its incidence. Many findings well established in systemic lymphoma remain to be investigated in OAL.

New pathogenetic data relate OAL to infectious chronic antigen stimulation by at least two organisms and may allow for less toxic therapeutic possibilities. In addition, these data may help explain the relatively high incidence of OAL in the ocular adnexae, which has limited resident lymphoid tissue. Immunotherapies have been used in combined modality treatment of OAL, but their efficacy is not yet known. Longer follow-up is needed to assess the effect of all

therapies used. Among low-grade OAL, recurrences are common, but tumor-related mortality is low.

Variability in study design has limited the information on this common ocular adnexal lesion. A standardized approach of analysis stratifying the cases by the initial extent of disease, classification, stage, treatment, molecular genetic status, and immunophenotypic profile should lead to better understanding of this disease and the elimination of spurious results based on small series.

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