Evidence is insufficient to recommend chemotherapy, immunotherapy, or antibiotics as initial treatment for localized extranodal marginal zone B-cell lymphoma of the ocular adnexa.

Extranodal Marginal Zone B-cell Lymphoma of the Ocular Adnexa

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Background: Low-grade B-cell lymphomas located around the eye present unique challenges in diagnosis and treatment. Extranodal marginal zone B-cell lymphoma is the most common lymphoma of the ocular adnexa (conjunctiva, orbit, lacrimal gland, and eyelid).

Methods: A systematic search of the relevant literature was performed. Material pertinent to the diagnosis, prognosis, pathogenesis, and treatment of extranodal marginal zone B-cell lymphoma of the ocular adnexa was identified, reviewed, and analyzed, focusing on management strategies for primary localized disease.

Results: The primary cause of extranodal marginal zone B-cell lymphoma of the ocular adnexa remains elusive, although an infectious agent is suspected. Radiotherapy is the most common initial treatment for localized disease. Initial treatment with chemotherapy, immunotherapy, and antibiotics has shown promising results, but the number of series is limited and controlled trials do not exist.

Conclusions: Although the long-term outcome of localized extranodal marginal zone B-cell lymphoma of the ocular adnexa is good, optimal treatment remains a goal. The variation in rates of local and systemic relapse among treated stage 1E tumors suggests that critical factors affecting outcomes are not fully understood. Radiotherapy is the standard of care; at this time, the evidence is insufficient to recommend chemotherapy, immunotherapy, or antibiotics for initial treatment of extranodal marginal zone B-cell lymphoma localized to the ocular adnexa. Well-controlled comparative studies are needed.

Introduction

Lymphomas are the most common malignancy of the orbit and lacrimal gland, ranking third behind squamous cell carcinoma and melanoma among the malignancies of the conjunctiva. The eyelid is an uncommon site of primary lymphoma and is more often secondarily involved when tumors spread from the conjunctiva or orbit. The incidence of ocular adnexal lymphoma has increased in recent decades, primarily due to an increase in extranodal marginal zone B-cell lymphoma of the mucosal-associated lymphoid tissue (MALT) type. Most types of lymphoma have been reported in periocular tissues, of which 95% or more are B cell in origin; extranodal marginal zone B-cell lymphoma is the most frequent, making up approximately 70% of cases, followed by follicular lymphoma and diffuse large B-cell lymphoma. Extranodal...
Marginal zone B-cell lymphoma of the ocular adnexa shares similar features with extranodal marginal zone B-cell lymphoma located elsewhere, including general morphology and immunophenotype, and, presumably, pathogenesis. Extranodal marginal zone B-cell lymphoma of the ocular adnexa is a presumed antigen-driven neoplasm based on the model of gastric extranodal marginal zone B-cell lymphoma. The putative antigenic stimulus (or stimuli) is a subject of investigation.

We provide a general overview of extranodal marginal zone B-cell lymphoma of the ocular adnexa, emphasizing key similarities and differences in biological behavior and management with other MALT-type lymphomas in different locations. Because most cases of extranodal marginal zone B-cell lymphoma of the ocular adnexa present as localized disease, this subset of patients with lymphoma will be the focus of clinical management in this article. Therapeutic studies were included if the researchers examined single treatment protocols for localized extranodal marginal zone B-cell lymphoma of the ocular adnexa (Ann Arbor stage IE).

To avoid omitting studies containing valuable clinical information on the treatment of localized extranodal marginal zone B-cell lymphoma, inclusion criteria allowed series with up to 15% of cases with disease located at other sites as long as outcomes were not collectively reported.

**Diagnosis**

The histological features of extranodal marginal zone B-cell lymphoma are similar to those of MALT-type lymphomas in general. Neoplastic lymphocytes consist of varying combinations of small cells resembling centrocytes, plasmacytoid lymphocytes, and monocytoid B cells, with fewer numbers of scattered large cells resembling centroblasts or immunoblasts. This heterogeneous population of cells is usually found among reactive follicles, some of which may eventually be overrun by lymphoma cells (follicular colonization). Plasma cells are prominent in some cases, and intranuclear pseudoinclusions (Dutcher bodies) are sometimes noted. Characteristic infiltration of the epithelium by neoplastic lymphocytes (lymphoepithelial lesion) is uncommon, and, when observed, it is found in the lacrimal gland and conjunctiva but not the orbit.16,17 However, collections of atypical lymphocytes in conjunctival epithelium and lacrimal ducts similar to lymphoepithelial lesions are not specific for extranodal marginal zone B-cell lymphoma. They have also been described in reactive processes of the conjunctiva and lacrimal gland.16 Monocytoid cells with abundant pale cytoplasm are observed less often in extranodal marginal zone B-cell lymphoma of the ocular adnexa than other sites.11 Transformation to diffuse large B-cell lymphoma should be considered when solid or sheet-like proliferations of large cells are encountered. These larger cells are usually positive for B-cell chronic lymphocytic leukemia/lymphoma (BCL) 6 and sometimes cluster designation (CD) 10.17

Given the morphological overlap between reactive lymphoid hyperplasia and extranodal marginal zone B-cell lymphoma, ancillary tests are often used to enhance diagnostic certainty. Extranodal marginal zone B-cell lymphomas are positive for CD20, BCL2, paired box 5 (PAX5), and CD79A but typically do not express CD5, CD10, or CD23.16 Fewer than 5% of cases express CD5.11,14,16 In the setting of CD5 positivity, the differential diagnosis might include mantle cell lymphoma (positive for cyclin D1, (t[11;14] present) and small lymphocytic lymphoma (positive for CD23).14 CD43 expression is less common in extranodal marginal zone B-cell lymphoma of the ocular adnexa compared with the salivary glands (12%–25% vs 70%).11,18 Lymphoma cells typically express immunoglobulin (Ig) M and are IgD negative; on average, the proliferation index is 15% by Ki-67 immunostaining.19

The immunohistochemical demonstration of light-chain restriction using formalin-fixed, paraffin-embedded tissue is challenging because detection of cytoplasmic light chains in nonplasmacytic proliferations is prone to false-negative testing.20,22 An alternative approach to demonstrating light-chain restriction is flow cytometry, which requires fresh tissue.23,24 Flow cytometry may also be useful in confirming immunophenotype, particularly when the size of a specimen is limited.23,24 Recurrent structural genetic abnormalities have been identified in MALT-type lymphomas, and the frequency of these alterations vary, depending on anatomical site.25 Although it is not specific, trisomy of chromosome 3 is the most commonly reported cytogenetic finding among MALT-type lymphomas.25 Among the common sites of MALT lymphomas, t(14;18)(q32;q21) involving IgH and MALT1 is the most frequently seen in the ocular adnexal MALTomas.26 This translocation has been reported in about 25% of cases in some series.26 Clonality of B cells can be documented by polymerase chain reaction (PCR) of Ig heavy chain.27,28

More centers are employing combinations of immunohistochemistry, flow cytometry, and PCR to diagnosis low-grade lymphoma and relying less on morphology alone.29

**Clinical Staging**

The approach to staging ocular adnexal lymphoma is similar to that for lymphoma in general, and typically includes thorough clinical and laboratory examinations with bone marrow biopsy.30 Although computed tomography (CT) or magnetic resonance imaging (MRI) with contrast is valuable to determining the extent of local disease of the orbit, eyelid, and paranasal sinuses, positron emission tomography (PET) may be superior for the initial staging of ocular adnexal lymphoma.
phoma. When compared with CT, use of PET has upstaged a majority of patients with ocular adnexal lymphoma. Evidence suggests that subclinical involvement of the eye can occur in persons with periocular lymphoma. In a study of ocular adnexal lymphomas, 25 study patients with bilateral involvement had uveal thickening with ocular B-scan ultrasonography. (Intraocular disease might have been missed if staging were based on CT alone.) Although uveal involvement with extranodal marginal zone B-cell lymphoma has been previously reported, few studies have documented how often it goes unrecognized when patients present with conjunctival and orbital disease. How uveal involvement might affect prognosis is also unclear.

Roughly two-thirds of ocular adnexal lymphomas are stage IE (localized extranodal tumors) using the Ann Arbor system. This disproportionate accumulation of cases in a single stage limits the discriminatory potential to forecast outcomes. Other shortcomings exist to the Ann Arbor system for ocular adnexal lymphoma, including the inability to take into account multicentric and bilateral tumors, extent of localized tissue involvement, and precise anatomical location around the eye. Application of the tumor, node, metastasis (TNM)–based system incorporating information on extent of disease within anatomical compartments of the ocular adnexa, bilateral nature, and information on regional lymph-node involvement may better predict outcome (Table 1). An initial study showed that tumor stage may more thoroughly describe the extent of disease, although it does not yet predict rate of relapse or survival. Stages N1 to N4 and M1 are associated with worse rates of survival. In a multicenter study using the TNM system, any prognostic utility ascribed to size and location of ocular adnexal lymphoma was eclipsed by histological classification and type of treatment. The capability of the TNM system to predict worse outcomes appears to reside in its ability to identify bilateral disease and to delineate nodal and metastatic involvement at the time of presentation.

The full potential of the TNM system may not be realized until it is modified to include additional biomarkers and when

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Primary Tumor</th>
<th>Pathological Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Lymphoma extent not specified</td>
<td>TX</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of lymphoma</td>
<td>T0</td>
</tr>
<tr>
<td>T1</td>
<td>Lymphoma involving the conjunctiva alone without orbital involvement</td>
<td>T1</td>
</tr>
<tr>
<td>T1a</td>
<td>Bulbar conjunctiva only</td>
<td>T1a</td>
</tr>
<tr>
<td>T1b</td>
<td>Palpebral conjunctiva ± fornix ± caruncle</td>
<td>T1b</td>
</tr>
<tr>
<td>T1c</td>
<td>Extensive conjunctival involvement, both bulbar and nonbulbar</td>
<td>T1c</td>
</tr>
<tr>
<td>T2</td>
<td>Lymphoma with orbital involvement ± any conjunctival involvement</td>
<td>T2</td>
</tr>
<tr>
<td>T2a</td>
<td>Anterior orbital involvement (± conjunctival involvement) but no lacrimal gland involvement</td>
<td>T2a</td>
</tr>
<tr>
<td>T2b</td>
<td>Anterior orbital involvement (± conjunctival involvement) plus lacrimal involvement</td>
<td>T2b</td>
</tr>
<tr>
<td>T2c</td>
<td>Posterior orbital involvement (± conjunctival involvement ± anterior orbit involvement and ± any extraocular muscle involvement)</td>
<td>T2c</td>
</tr>
<tr>
<td>T2d</td>
<td>Nasolacrimal drainage system involvement (± conjunctival involvement but not including nasopharynx)</td>
<td>T2d</td>
</tr>
<tr>
<td>T3</td>
<td>Lymphoma with preseptal eyelid involvement ± orbital involvement ± any conjunctival involvement</td>
<td>T3</td>
</tr>
<tr>
<td>T4</td>
<td>Orbital adnexal lymphoma extending beyond orbit to adjacent structures such as bone and brain</td>
<td>T4</td>
</tr>
<tr>
<td>T4a</td>
<td>Involvement of nasopharynx</td>
<td>T4a</td>
</tr>
<tr>
<td>T4b</td>
<td>Osseous involvement (including periosteum)</td>
<td>T4b</td>
</tr>
<tr>
<td>T4c</td>
<td>Involvement of maxillofacial, ethmoidal, and/or frontal sinuses</td>
<td>T4c</td>
</tr>
<tr>
<td>T4d</td>
<td>Intracranial spread</td>
<td>T4d</td>
</tr>
</tbody>
</table>

**Regional Lymph Nodes**

| NX            | Regional lymph nodes cannot be assessed | NX           |
| N0            | No evidence of lymph node involvement   | N0           |
| N1            | Involvement of ipsilateral regional lymph nodes (preauricular, parotid, submandibular, and cervical) | N1           |
| N2            | Involvement of contralateral or bilateral regional lymph nodes | N2           |
| N3            | Involvement of peripheral lymph nodes not draining; ocular adnexal regional | N3           |
| N4            | Involvement of central lymph nodes      | N4           |

**Distant Metastasis**

| M0            | No evidence of involvement of other extranodal sites (no pathologic M0; use clinical M to complete stage group) | M0           |
| M1a           | Noncontiguous involvement of tissues or organs external to the ocular adnexa (eg, parotid glands, submandibular gland, lung, liver, spleen, kidney, breast) | M1a          |
| M1b           | Lymphoma involvement of the bone marrow | M1b          |
| M1c           | Both M1a and M1b | M1c          |

new imaging technologies can be used to help provide superior metrics in terms of tumor location and volume.

Pathogenesis
Infectious agents have been suspected in the etiology of extranodal marginal zone B-cell lymphoma of the ocular adnexa based on the causative role that *Helicobacter pylori* infection plays in gastric MALT-type lymphoma. The progression of *H pylori*–induced chronic gastritis to extranodal marginal zone B-cell lymphoma is comprehensible both in terms of light microscopy and molecular changes. Unlike malignant transformation of lymphocytes through the direct infection of lymphotropic viruses like Epstein–Barr virus or human T-cell leukemia virus type 1, *H pylori* indirectly acts by inducing chronic inflammation. This antigen-driven process, coupled with other oncogenic events, can lead to the emergence of antigen-independent lymphocyte proliferation.

**Chlamydia psittaci**
The search for putative infectious agents for periocular lymphoma has resulted in conflicting results. Using PCR, an Italian study found that 80% of patients with extranodal marginal zone B-cell lymphoma of the ocular adnexa were exposed to *Chlamydia psittaci*. However, similar investigations from other regions of the world could not duplicate these results. In a review of 11 international studies, the overall rate of *Chlamydia* positivity in extranodal marginal zone B-cell lymphoma of the ocular adnexa was 23%, with the vast majority of all positive cases (90%) occurring in 3 countries. In a survey of 423 cases of extranodal marginal zone B-cell lymphoma of the ocular adnexa, the detection rate of *Chlamydia* ranged from 0% to 87%, with seemingly inconsistent geographic variation. To control for spurious laboratory results, investigators used a single standardized procedure for *Chlamydia* DNA detection among 142 cases of extranodal marginal zone B-cell lymphoma of the ocular adnexa. The results confirmed a variation in prevalence (eg, 11% in southern China, 47% in Germany); the overall prevalence of *C psittaci* DNA was 22%, which was more than twice the control group (10%; *P* = .04). However, based on historical prevalence, this result was not much greater than that established for non-neoplastic disorders of the orbit.

**Helicobacter pylori**
The causal association between *H pylori* infection and gastric extranodal marginal zone B-cell lymphoma is well established, so investigators have begun searching for a link between the bacterium and extranodal marginal zone B-cell lymphoma of the ocular adnexa. Chan et al described *H pylori* DNA in 4 of 5 cases of conjunctival extranodal marginal zone B-cell lymphomas using PCR amplification and Southern blot hybridization. The DNA of *H pylori* was not found in normal conjunctiva from the same study patients. The same group examined 8 study patients with orbital extranodal marginal zone B-cell lymphoma and found 1 study patient with the genomic fingerprints of *H pylori*. C pneumoniae (but not *C psittaci* or *C trachomatis*) was identified in another.

Lee et al identified DNA of *H pylori* in 15 of 15 cases of extranodal marginal zone B-cell lymphoma of the conjunctiva that they examined; no such discovery was made in the control group (n = 8). These findings contrast with another study involving 13 cases of extranodal marginal zone B-cell lymphoma of the conjunctiva in which *H pylori* DNA could not be detected in any tumor (either using immunohistochemistry or PCR).

The prevalence of gastric *H pylori* infection at the time of initial diagnosis of extranodal marginal zone B-cell lymphoma varies between where the primary site of lymphoma is located. For example, the prevalence rate of infection was found to be 45% (37 of 83 cases) in extranodal marginal zone B-cell lymphoma of the ocular adnexa compared with 25% (25 of 101 cases) in extranodal marginal zone B-cell lymphoma located elsewhere (but not the stomach). The rate of prevalence was 12% (18 of 156) among control cases without lymphoma. These findings led investigators to propose another pathogenic mechanism involving the attraction of circulating lymphomatous cells to the ocular adnexa. Once around the eye, the lymphocytes would then be transformed under the influence of additional mitogenic stimuli. This study and the proposed hypothesis has generated need for further investigation.

**Other Infectious Agents**
An international study investigating the presence of viral DNA for herpes simplex virus types 1 and 2 and adenovirus types 8 and 19 in persons with extranodal marginal zone B-cell lymphoma of the ocular adnexa found no association. Although the conceptual model of an infectious etiology is appealing, consistent and reproducible evidence supporting any specific pathogen has been elusive.

**Autoimmunity**
The possibility of an autoantigenic stimulus is supported by the association of extranodal marginal zone B-cell lymphoma of the ocular adnexa with various autoimmune disorders (eg, Sjögren disease, Hashimoto disease, IgG4-related disorder). The connection between Sjögren disease and lymphoma has been known since the 1970s. Although Sjögren disease conveys a 10-fold greater risk of B-cell lymphoma, the cause for...
this susceptibility is unclear. Several cases of extranodal marginal zone B-cell lymphoma of the ocular adnexa have been reported in persons with IgG4-related disease — an association that provides little additional insight into pathogenesis.

**Treatment**

A comprehensive review of treatment options for extranodal marginal zone B-cell lymphoma of the ocular adnexa is beyond the scope of this review. Most therapeutic studies have consisted of retrospective case series. Comparing clinical outcomes in these nonrandomized trials is perilous for several reasons. Clinical series of ocular adnexal lymphoma published prior to 2000 often lumped extranodal marginal zone B-cell lymphoma together with other low-grade lymphomas and atypical lymphoid hyperplasia. Even large studies involving 2 or more treatment arms had limited statistical power to exclude small but meaningful differences in outcome. The success of local therapy is often confounded by supplemental treatment given to partial responders because clinical outcomes are collectively reported. In addition, short-term studies (< 5 years) may also not adequately reflect the biological potential of the disease, particularly in terms of rates of local and systemic recurrence, and tumor-related mortality.

**Radiotherapy**

Typically, radiotherapy results in a high rate of local control that ranges from 85% to 100%, even in the presence of systemic disease. Since 2000, a total of 9 studies have examined the outcome of radiotherapy for localized extranodal marginal zone B-cell lymphoma of the ocular adnexa (Table 2). Some included small numbers of study patients with systemic disease, and clinical outcomes were measured in ways that prohibit uniform summarization. The majority of the 503 study patients with stage 1E disease achieved local control. When reported, complete response (CR) rates ranged from 52% to 93%, whereas the proportion of 5-year, systemic-free relapse rates usually exceeded 90%. Overall, systemic relapses occurred in 31 study patients (6.2%), ranging from a low rate of 2.2% (median follow-up of 32 months) to a high rate of 16.8% (median follow-up of 5.9 years).

However, these results must be interpreted with caution because the methods and rigor used to detect recurrent disease differed and the protocols employed to treat partial response and recurrence varied. The different types of second-line therapies for incomplete localized responses confound the direct comparison of clinical series, particularly in terms of rates of systemic recurrence and tumor-related deaths.

**Chemotherapy**

Use of chemotherapy for local ocular adnexal disease has been studied in 2 centers (n = 54); of the patients studied, 52 had stage 1E disease (Table 3). Among 21 study patients (19 [90%] with stage 1E) treated with cyclophosphamide, vincristine, and prednisolone, CR was reported in 16 (76%), local relapse occurred in 5, and systemic relapse occurred in 2; no deaths were reported during a median follow-up time of 55 months.

The other trial studied chlorambucil in 33 participants with stage 1E extranodal marginal zone B-cell lymphoma. During a median follow-up of 26 months, CR was reported in 26, local recurrence in 1, and systemic relapse in 3; 1 tumor-related death was noted. Proponents of initial chemotherapy state that this treatment option eliminates local complications from radiotherapy, such as dry eyes, cataracts, and skin irritation, and is associated with fewer serious complications. Direct comparison with radiotherapy for stage 1E disease is methodologically problematic, because some reports include small proportions of study patients with more advanced disease. The collective rate of systemic relapse for radiotherapy is 6.2%, which is less than that currently reported for chemotherapy (9.3%; see Tables 2 and 3).

**Immunotherapy**

Rituximab, a chimeric mouse antihuman CD20 monoclonal antibody, has been used as treatment for lymphoma localized to the ocular adnexa. Two reports involving 12 study patients with localized extranodal marginal zone B-cell lymphoma have been published (see Table 3). In one study, 11 eyes of 10 study patients with ocular adnexal lymphoma were treated with systemic rituximab. CR was reported in 5 (56%; median follow-up of 31 months) without systemic or ocular adverse events, and no tumor-related deaths were reported. The remaining study patients required radiotherapy. Another report involved 5 study patients with extranodal marginal zone B-cell lymphoma of the ocular adnexa, 3 of whom had stage 1E disease. Four of the 5 study patients who initially responded to treatment locally relapsed.

To date, rituximab has been reported in relatively few patients with extranodal marginal zone B-cell lymphoma localized to the ocular adnexa, with seemingly high rates of inadequate periocular response and local recurrence (see Table 3). The median follow-up times (< 31 months) are too short to assess the role of rituximab as therapy for local disease at this time.

**Antibiotic Therapy**

Because some cases of extranodal marginal zone B-cell lymphoma of the ocular adnexa have been associated with infection, treatment with doxycycline has been attempted. A meta-analysis of 4 treatment...
trials taking place prior to 2006 totaling 42 study patients found that 20 responded to oral antibiotics, 20 remained stable, and 2 progressed.\(^\text{47}\) Although CR was reported in 8 study patients, objective responses with radiography or slit lamp photography were available in 3.\(^\text{47}\)

Since 2006, researchers have initiated 3 trials to study the effect of doxycycline on the management of predominantly primary extranodal marginal zone B-cell lymphoma localized to the ocular adnexa in 151 study patients (Table 4).\(^\text{76,78,85-87}\) Because the rate of tumor response (ie, reduction in size) differs following treatment with doxycycline and radiotherapy or chemotherapy, it is difficult to directly measure and compare clinical outcomes.\(^\text{76,85,87}\) One study reported a 2-year failure-free survival rate of 67%,\(^\text{89}\) whereas an-
### Table 3. — Chemotherapy or Immunotherapy for Localized Extranodal Marginal Zone Lymphoma of the Ocular Adnexa

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>No. of Study Patients</th>
<th>Location Stage Cases of Local Relapse</th>
<th>Cases of Systemic Relapse</th>
<th>Median Follow-Up, mo</th>
<th>Other Outcome Measures</th>
<th>No. of Tumor-Related Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ben Simon⁶⁹</td>
<td>Chlorambucil</td>
<td>33</td>
<td>Orbit: 10 Lacrimal gland: 8 Conjunctiva: 7 Eyelid: 6 Combination: 2</td>
<td>1E: All</td>
<td>1</td>
<td>3</td>
<td>26 (range, 8–62)</td>
</tr>
<tr>
<td>Song⁶⁸</td>
<td>Cyclophosphamide Vincristine Prednisolone</td>
<td>21</td>
<td>Conjunctiva: 6 Orbit: 8 Eyelid: 5 Lacrimal gland: 2 Adnexa (general): 2</td>
<td>1E: 19 Bilateral: 2 IIE: 2</td>
<td>5</td>
<td>2</td>
<td>58 (range, 6–163)</td>
</tr>
<tr>
<td><strong>Immunotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferreri⁶⁷</td>
<td>Rituximab</td>
<td>5</td>
<td>Conjunctiva: 2 Orbital: 1</td>
<td>1E: 3 IV: 2</td>
<td>4</td>
<td>1</td>
<td>23 (range, 2–4)</td>
</tr>
<tr>
<td>Tuncer⁶¹</td>
<td>Rituximab</td>
<td>9</td>
<td>Conjunctiva: 5 Bilateral: 1 Orbital: 4</td>
<td>1E: All</td>
<td>6</td>
<td>None</td>
<td>31 (range, 10–61)</td>
</tr>
</tbody>
</table>

⁶Includes series with ≥ 2 study patients with disease beyond the orbit.
⁷Local relapse defined as any portion of ocular adnexa, including the contralateral side, of initial unilateral disease.
CR = complete response, PR = partial response.

### Table 4. — Antibiotic Therapy or Observation for Extranodal Marginal Zone Lymphoma of the Ocular Adnexa

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>No. of Study Patients</th>
<th>Location Stage Cases of Local Relapse</th>
<th>Cases of Systemic Relapse</th>
<th>Median Follow-Up, mo</th>
<th>Other Outcome Measures</th>
<th>No. of Tumor-Related Deaths</th>
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</thead>
<tbody>
<tr>
<td><strong>Antibiotic Therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferreri⁶⁵</td>
<td>Doxycycline</td>
<td>27</td>
<td>Conjunctiva: 14 Orbit: 13</td>
<td>1E: 24 IIIE: 3 Bilateral: 5</td>
<td>Unable to determine local from systemic relapses</td>
<td>21 mo (range, 4–204)</td>
<td>Overall response: 64% 2-y failure-free survival: 67%</td>
</tr>
<tr>
<td>Ferreri⁶⁷</td>
<td>Doxycycline</td>
<td>34</td>
<td>Conjunctiva: 23 Orbit: 14 Lacrimal gland: 5 Conjunctiva/orbit: 5</td>
<td>1E: All</td>
<td>14 failures Unable to delineate local from systemic</td>
<td>37 mo (range, 15–62)</td>
<td>5-y PFS: 55%</td>
</tr>
<tr>
<td>Han⁷⁸</td>
<td>Doxycycline</td>
<td>90</td>
<td>Conjunctiva: 74 Orbit: 12 Eyelid: 3 Lacrimal gland: 2 T1N0M0: 62 T2N0–2 M0: 22 T3N0–2 M0: 5 T4N0M0: 1</td>
<td>31</td>
<td>6</td>
<td>40.5 mo (range, 8–85)</td>
<td>5-y PFS: 61%</td>
</tr>
<tr>
<td><strong>Observation Without Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matsuo⁷⁶</td>
<td>None other than biopsy</td>
<td>8c</td>
<td>Conjunctiva: 8 1E: All None None 5.4 y (range, 1–11)</td>
<td>7 spontaneously regressed</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanimoto⁶⁶</td>
<td>None other than biopsy</td>
<td>36</td>
<td>Conjunctiva: 15 Orbit: 19 Lacrimal gland: 2 1E: 36 Bilateral: 5</td>
<td>15</td>
<td>2</td>
<td>10.5 y (range, 0.7–16.7)</td>
<td>OS: 5-y: 94% 10-y: 94% 15-y: 71%</td>
</tr>
</tbody>
</table>

⁴Includes series with ≥85% localized stage 1E extranodal marginal zone B-cell lymphoma since 2000.
⁵Local relapse defined as any portion of the ocular adnexa, including the contralateral side, of initial unilateral disease.
⁶Eight of 13 study patients who declined treatment and are the focus of this review.
OS = overall survival, PFS = progression-free survival.
other series reported that the failure-free survival rate after 5 years was 55%. Progressive disease was treated with a variety of traditional protocols, and no tumor-related deaths were reported (see Table 4). In that study, patients were excluded from the trial if they had large tumors or tumors demonstrating rapid growth. Because criteria describing large tumor size and rapid growth were not provided, an exclusion bias of unknown clinical importance complicates any interpretation of these results.

Long-term follow-up in 1 study of 90 patients initially treated with doxycycline had mixed results. Patients enrolled in the clinical trial received twice-daily oral 100 mg doxycycline for either 3 or 6 weeks and were followed for a mean time of 40.5 months. A total of 61% had no progression after 5 years, and 34 study patients who failed doxycycline therapy were successfully managed with chemotherapy, radiotherapy, or both. No tumor-related deaths were reported; systemic relapse was reported in 6 study patients. Pretreatment exposure to \( C. psittaci \) was not determined.

"Failed to progress" reports are difficult to compare to studies whose benchmark outcomes are either complete or partial regression, and this is particularly true for cases of lymphoma with an indolent course. Lacking or incomplete knowledge of a history of chlamydial infection among patients enrolled in antibiotic studies further complicates interpretation, because the global variation in \( C. psittaci \) infection rate should affect the response rate to doxycycline. Future trials of antibiotic treatment may be more efficient if their enrollment is appropriately limited to patients with documented exposure to \( C. psittaci \).

A 6-month trial of a second-line therapeutic agent, clarithromycin, was reported in a trial of 7 study volunteers who had extranodal marginal zone B-cell lymphoma that failed to respond to doxycycline. Partial response was reported in 4 study patients and stable disease for varying periods of time was reported in 3; however, all study patients experienced disease progression (average time to progression, 16 months).

**Observation**

Given the indolent nature of extranodal marginal zone B-cell lymphoma of the ocular adnexa, some investigators have wondered whether observation may be a viable option, particularly in persons of advanced age or with other comorbidities that may limit survival. Two groups reported on the long-term follow-up data of 44 study patients with localized disease (5 bilateral); the median follow-up periods were 5.4 years and 10.5 years. Twenty-five (57%) study patients did not require treatment throughout the course of the study, and 2 succumbed to progressive lymphoma. A total of 17 study patients (39%) progressed; transformation to high-grade lymphoma occurred in 1 case. The majority of tumors arose in conjunctiva (23 [52%]), 7 of which spontaneously regressed. Therefore, the study authors concluded that watchful waiting might be an acceptable option in select patients with unilateral extranodal marginal zone B-cell lymphoma of the ocular adnexa.

**Assessment of Clinical Outcome**

Comparing the treatment of primary lymphoma localized to the ocular adnexa is difficult because some series combine different histological types of lymphoma, some researchers do not separately analyze for anatomical subgroups (eg, conjunctiva, orbit), and some report clinical outcomes differently. In addition, not all studies employ standardized intervals for follow-up or methods for monitoring outcome (eg, CT, MRI, PET/CT, PET). Few provide information on primary tumor size, and most employ different salvage therapies for partial responders.

Tumor size is an important parameter to monitor because the rapidity and completeness with which a tumor shrinks may correlate with durability of response. However, the speed at which tumor size is reduced may be of less importance in cases of low-grade lymphoma compared with other neoplasms, and it may be of less value in terms of assessing antibiotic effectiveness. Use of tumor diameter — not volume — as an outcome variable for extranodal marginal zone B-cell lymphoma of the ocular adnexa reflects how difficult it is to obtain reliable volumetric data on periorcular tumors in general.

Measuring the volume or planar dimensions of periorcular tumors presents unique challenges. For example, oftentimes, lymphomas of the ocular adnexa are irregularly shaped and conform to the contours of the eye and orbital walls. It might be valuable to apply the Response Evaluation Criteria in Solid Tumors (RECIST) and RECIST 1.1 to these lesions, but these criteria have not been independently validated in the context of low-grade lymphoma of the ocular adnexa.

One of the few studies that addressed the role of quantitative, monitored outcomes in the setting of extranodal marginal zone B-cell lymphoma of the ocular adnexa following radiotherapy was performed by Jung et al. These researchers found that the maximum tumor diameter decreased by 50% of its initial size after 4.7 months of treatment. The authors emphasize that partial and total responses are usually poorly defined in most clinical series — both in terms of tumor-specific size reductions and in follow-up intervals after treatment.

**Conclusions**

Extranodal marginal zone B-cell lymphoma of the ocular adnexa can arise in the setting of reactive lymphoid
hyperplasia, but the underlying cause of this presumed antigen-driven process is unclear. Given the epidemiological results to date, a more complex interplay of putative infectious agents and immune response is possible. In terms of treatment options for primary localized extranodal marginal zone B-cell lymphoma of the ocular adnexa, radiotherapy provides good local control and is associated with relatively low systemic spread. Studies assessing the effectiveness of other initial treatment options for localized disease (eg, chemotherapy, immunotherapy, antibiotics) are limited by several weaknesses, including small study size, enrollment biases, and imbalanced mixtures of anatomical locations (ie, lacrimal gland, conjunctiva, eyelid, orbit). The evidence is insufficient at this time to recommend an alternative to radiotherapy for primary localized extranodal marginal zone B-cell lymphoma of the ocular adnexa.

As more optimal therapies are sought and randomized clinical trials remain unlikely, future investigations might consider use of methodologies to volumetrically measure tumor response, to establish standardized protocols for initial evaluation and follow-up, and to use equivalent rescue protocols for partial responses so that different clinical series can be compared against one another.

References


