Prevalence and Nature of Systemic Involvement and Stage at Initial Examination in Patients With Orbital and Ocular Adnexal Lymphoma

Elham Hatef, MD; Dianna Roberts, PhD; Peter McLaughlin, MD; Barbara Pro, MD; Bita Esmaeli, MD

Objective: To determine the stage at initial examination and the prevalence of systemic involvement in patients with orbital and ocular adnexal lymphoma.

Methods: The medical records of all patients with orbital and ocular adnexal lymphoma treated in a recent 7-year period were reviewed for stage at initial examination, highest stage during the follow-up period, and recurrence-free survival.

Results: Forty-three patients were included. Nineteen patients had mucosa-associated lymphoid tissue, 9 had follicular, 9 had diffuse large-cell, 3 had mantle cell, 2 had small lymphocytic, and 1 had large T-cell lymphoma. The staging workup included chest radiography; orbital computed tomography or magnetic resonance imaging; computed tomography of the chest, abdomen, and pelvis; and bone marrow biopsy. Thirty-six patients had total body positron emission tomography, 7 had gallium scans, and 16 had gastrointestinal endoscopy. Lymphoma stage at diagnosis was IE in 18 patients, II in 6, and IV in 19. Six of 19 patients with mucosa-associated lymphoid tissue, 7 of 9 patients with follicular, 6 of 9 patients with diffuse large-cell, and 3 of 3 patients with mantle cell lymphoma had non–stage IE disease at initial examination. The 5-year recurrence-free survival was 64.6% for the entire cohort.

Conclusions: Extraorbital involvement is present at diagnosis in more than half of patients with orbital and ocular adnexal lymphoma and warrants extensive systemic workup at diagnosis, continued surveillance, and consideration of systemic therapy.

Arch Ophthalmol. 2007;125(12):1663-1667

ORBITAL AND OCULAR ADNEXAL LYMPHOMA accounts for only about 2% of all cases of non-Hodgkin lymphoma but is the most common primary orbital malignancy in adults. Orbital and ocular adnexal lymphomas can involve the orbit, the eyelid, the conjunctiva, or a combination of these 3 ocular adnexal structures. The most common histologic subtype of orbital and ocular adnexal lymphoma is mucosa-associated lymphoid tissue (MALT) lymphoma; the second most common subtype is low-grade follicular lymphoma. Diffuse large-cell lymphoma, mantle cell lymphoma, and other more aggressive histologic subtypes are less commonly seen in the orbital and ocular adnexal structures. Most investigators believe that orbital and ocular adnexal lymphomas are associated with a very low rate of systemic involvement. For this reason, most investigators do not recommend extensive staging workup at the time of initial diagnosis or during the follow-up period. In addition, because of beliefs about a low rate of systemic involvement in orbital and ocular adnexal lymphoma, irradiation of the ocular adnexal structures has historically been considered standard treatment for this disease. A few studies have suggested that a detailed and accurate staging workup at diagnosis of orbital and ocular adnexal lymphoma is critical, because the presence of extraorbital disease is associated with a poor prognosis. Most studies to date, however, have focused on the initial ophthalmic signs and symptoms and have promoted local radiation therapy for low-grade orbital and ocular adnexal lymphoma without much attention to detailed staging information. Some evidence suggests that MALT lymphomas are indolent and associated with a very good prognosis; other evidence suggests no difference in survival between patients with MALT lymphoma and those with other low-grade forms of orbital and ocular adnexal lymphoma. The goal of our study was to determine the disease stage at initial examination.
tion and the prevalence and nature of systemic involve-
ment at initial examination and during the follow-up
period for each histologic subtype of orbital and ocular
adnexal lymphoma. This retrospective study was lim-
ited to patients who underwent staging at a single ter-
iary cancer center, which followed a uniform lymph-
oma staging protocol, and whose lymphoma was diag-
osed during a recent period when advanced stag-
ing tools, such as positron emission tomography, were
available. Appropriate institutional review board ap-
proval was obtained for this study.

**METHODS**

**DATA COLLECTION**

The medical records of all patients with a diagnosis of orbital
and ocular adnexal lymphoma treated by the senior author (B.E.)
between January 1999 and October 2006 at a single tertiary can-
cer center were reviewed. During this period, all patients with
orbital and ocular adnexal lymphoma staging seen at our insti-
tution had a standard staging workup that included chest radiogra-
y; computed tomography (CT) or magnetic resonance imaging
(MRI) of the orbit; CT of the chest, abdomen, and pelvis; and
a bone marrow biopsy. Additional staging examinations were
ordered as indicated by the patient’s signs and symptoms at the
physician’s discretion.

For each patient, the following data were collected from
the patient’s medical record: age, sex, ethnicity, ocular and systemic
symptoms and signs at initial examination, anatomic site of in-
volve ment (orbit, eyelid, conjunctiva, or a combination of these
structures), laterality, histologic subtype of lymphoma, ele-
ments of the staging workup, stage of lymphoma at initial ex-
amination, highest stage during the follow-up period, site of sys-
temic involvement (if any) at diagnosis of lymphoma, initial
 treatment modality, response to therapy, site of recurrence (if any),
recurrence-free survival (RFS), follow-up time after diagnosis of
orbital and ocular adnexal lymphoma, and patient’s status at last
contact. Patients with perilocular mycosis fungoides were excluded.

The 5-year RFS rate was defined as the proportion of pa-
tients who neither died nor had any recurrence during the first
5 years after completion of treatment for orbital and ocular ad-
nexal lymphoma. Complete response was defined as complete
disappearance of all detectable clinical evidence of disease in
the orbit and ocular adnexa and disease-related symptoms if
present before therapy. The response to therapy was evalu-
ated using clinical examination and CT or MRI of the orbit.
Patient and Disease Characteristics

**RESULTS**

**PATIENT AND DISEASE CHARACTERISTICS
AND SYMPTOMS AT INITIAL EXAMINATION**

Forty-three patients with a diagnosis of orbital and ocular
adnexal lymphoma were treated by the senior author (B.E.)
during the study period. There were 26 women and 17 men,
ranging in age from 25 to 84 years (median, 62 years).
Twenty-eight patients (65%) had primary orbital and ocu-
lar adnexal lymphoma, ie, orbital and ocular adnexal lym-
phoma was the first and predominant site of involvement,
and 15 (35%) had secondary orbital and ocular adnexal lym-
phoma, ie, the diagnosis of ocular adnexal involvement fol-
lowed a previously established diagnosis of lymphoma. In
the 15 patients with secondary orbital and ocular adnexal
lymphoma, the time from diagnosis of lymphoma to diag-
nosis of ocular adnexal involvement ranged from 10.8 to
179.0 months (median, 52.4 months). Thirty-five pa-
tients (81%) had unilateral disease (affecting the right eye
in 20 patients and the left eye in 15) and 8 patients (19%)
had bilateral disease. Thirty-two patients (74%) had or-
bal involvement, 10 (23%) had conjunctival involve-
ment, and 7 (16%) had eyelid involvement. Five patients
had involvement of more than 1 ocular structure: 3 had
involvement of the orbit and conjunctiva; 1 had involve-
ment of the orbit, conjunctiva, and eyelid; and 1 had in-
volvement of the eyelid and orbit.

The symptoms at diagnosis of orbital and ocular ad-
nexal lymphoma included a palpable mass in the orbit
or eyelid in 14 patients (33%), eyelid or periorbital swelling
in 12 patients (28%), proptosis in 9 patients (21%),
diplopia in 8 patients (19%), upper eyelid ptosis in 4 pa-
tients (9%), excessive tearing in 4 patients (9%), fever,
weight loss, and/or night sweats in 4 patients (9%), and
an afferent pupillary defect suggesting significant optic
nerve compression due to the mass effect of orbital and ocular adnexal lymphoma in 2 patients (5%).

**HISTOLOGIC SUBTYPES OF ORBITAL AND OCULAR ADNEXAL LYMPHOMA**

At initial examination, 19 patients (44%) had MALT lymph-
oma (Table 1). Nine patients (21%) had follicular lymph-
oma: grade I or II (low grade) in 5 patients, grade III

**Table 1. Stage of Orbital and Ocular Adnexal Lymphoma by Histologic Subtype**

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>All</th>
<th>Stage IE</th>
<th>Stage II</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosa-associated lymphoid tissue lymphoma</td>
<td>19 (100)</td>
<td>13 (68)</td>
<td>1 (5)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>9 (100)</td>
<td>2 (22)</td>
<td>0</td>
<td>7 (77)</td>
</tr>
<tr>
<td>Diffuse large-cell lymphoma</td>
<td>9 (100)</td>
<td>3 (33)</td>
<td>5 (56)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>3 (100)</td>
<td>0</td>
<td>0</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma</td>
<td>2 (100)</td>
<td>0</td>
<td>0</td>
<td>2 (100)</td>
</tr>
<tr>
<td>B-chronic lymphocytic leukemia</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Large T-cell/natural killer cell lymphoma</td>
<td>18 6 19</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

©2007 American Medical Association. All rights reserved.
(high grade) in 1 patient, and an unspecified grade in 3 patients. Nine patients (21%) had diffuse large-cell lymphoma, 3 patients had mantle cell lymphoma, 2 patients had small lymphocytic lymphoma/B-chronic lymphocytic leukemia, and 1 patient had large T-cell/natural killer cell lymphoma.

STAGE OF ORBITAL AND OCULAR ADNEXAL LYMPHOMA AT INITIAL EXAMINATION AND DURING THE FOLLOW-UP PERIOD

In addition to the standard staging workup performed in every patient (chest radiography; CT of the chest, abdomen, and pelvis; and a bone marrow biopsy), 36 patients (84%) underwent total body positron emission tomography, and the other 7 (16%) had total-body gallium scans. Gastrointestinal endoscopy was done in 16 patients (37%), 13 of whom (81%) had MALT lymphoma. The incidence of gastrointestinal involvement is as high as 88% in patients with mantle cell lymphoma; thus, gastrointestinal endoscopy for mantle cell lymphoma is not routinely done at our institution, and it is assumed that patients with mantle cell lymphoma have gastrointestinal involvement.

At diagnosis of orbital and ocular adnexal lymphoma, 18 patients (42%) had stage IE disease, 6 patients (14%) had stage II disease, and 19 patients (44%) had stage IV disease (Table 1). Of the 28 patients with primary orbital and ocular adnexal lymphoma, 13 patients (46%) had stage IE, 5 patients (18%) had stage II, and 10 patients (36%) had stage IV lymphoma. Table 1 presents the stage of orbital and ocular adnexal lymphoma by histologic subtype.

Of the 25 patients with non–stage IE disease at diagnosis of orbital and ocular adnexal lymphoma, 14 (56%) had extranodal systemic involvement only, 4 (16%) had nodal systemic involvement only, 7 (28%) had both nodal and extranodal systemic involvement, and 4 (9%) had bone marrow involvement. Three of the 18 (17%) patients who initially had stage IE disease developed systemic nodal disease (stage IV) during the follow-up period.

Fourteen patients with primary orbital and ocular adnexal lymphoma underwent biopsy of extraorbital sites of systemic involvement. In 3 patients, the type of lymphoma in the ocular adnexal structures was different from that at the extraorbital site. One patient had diffuse large-cell lymphoma in the eyelid but large T-cell/natural killer cell lymphoma at the extraorbital site; 1 had low-grade follicular lymphoma in the eyelid but small lymphocytic lymphoma at the extraorbital site; and 1 had follicular lymphoma in the orbit and diffuse large-cell lymphoma in the extraorbital site.

TREATMENT OF ORBITAL AND OCULAR ADNEXAL LYMPHOMA

Table 2 summarizes the treatment modalities used in our patients. Sixteen patients had radiotherapy; of these, 8 had radiotherapy in combination with other forms of systemic treatment. Fourteen patients had various forms of chemotherapy, and 20 had monoclonal antibody therapy. One patient underwent bone marrow transplantation after treatment with systemic chemotherapy and rituximab. The most common combination chemotherapy was cyclophosphamide, doxorubicin, vincristine, and prednisolone, which was used in 7 of 14 patients who had systemic chemotherapy alone or in combination with other treatment modalities. Fractionated cyclophosphamide was used in 4 patients; mesna and fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone was used in 2 patients. The number of chemotherapy cycles ranged from 1 to 10 (median, 6). Twenty-five of 35 patients (71%) who completed treatment had a complete response, 6 (17%) had a partial response, and 5 (14%) had stable disease.

RFS, RECURRENCE RATES, AND MORTALITY RATES

The median follow-up time, from diagnosis of ocular adnexal lymphoma to death or last contact, for the 43 patients whose records were examined was 24 months (range, 0.3-142.1). Specific information about the chronology of initial treatment, recurrences, and mortality that was necessary for the RFS calculations was available for 36 of these patients (83.7%). For this subgroup, the median follow-up time was 27.8 months (range, 2.1-142.1). The RFS rate at 5 years for these 36 patients was 64.6% by the Kaplan-Meier method (Figure).

Ten patients had recurrences during the study period (median, 1 recurrence [range, 1-9]). Four patients had recurrence in the ocular adnexal structures; 3 patients had systemic recurrence; and 3 had both ocular adnexal and systemic recurrences. At last contact, 24 patients (56%) were alive with no detectable disease, 14 (33%) were alive with disease, 2 (5%) had died of the disease, and 3 (7%) had died of other causes.

Patients with primary orbital and ocular adnexal lymphoma had a higher 3-year RFS than those with secondary orbital and ocular adnexal lymphoma (79.7% vs 36.4%, respectively; \( P = .01 \)). The 5-year RFS rate was higher for MALT lymphoma patients compared with the rest of the patients with orbital and ocular adnexal lym-
To our knowledge, this is the first report of a series of patients with orbital and ocular adnexal lymphoma treated in an ophthalmology practice fully based at a comprehensive cancer center. Because of the unique makeup of the patients and the uniform practice patterns for staging of lymphoma at our institution, this relatively large series of patients with orbital and ocular adnexal lymphoma provides some interesting new insights.

Our most significant finding was that almost half of the patients with primary orbital and ocular adnexal lymphoma had non–stage IE disease at the time of initial diagnosis. In addition, 3 of 18 patients who initially had stage IE lymphoma developed systemic nodal involvement (stage IV disease) during the follow-up period. The distribution of histologic subtypes in our series is better detection of systemic disease than those who had nodal lymphoma (77.9% vs 29.4%, respectively; \( P = .01 \)).

The 5-year RFS was higher for patients who had a complete response to treatment than in those who had a partial response (82.6% vs 0%, respectively; \( P = .006 \)). Four of the 25 patients with a complete response died at 5 years, whereas 6 of 6 patients with a partial response died at 5 years.

Another interesting observation in our cohort is the treatments chosen for orbital and ocular adnexal lymphoma. Only 16 patients (37%) had orbital radiotherapy as the primary treatment modality; more than half of these patients received chemotherapy or monoclonal antibody therapy in combination with radiotherapy. More than half of the patients in this cohort were treated with monoclonal antibodies directed against CD20 (rituximab or ibritumomab tiuxetan). This recent trend of using monoclonal antibodies or monoclonal antibodies with a radioactive ligand (radioimmunotherapy) for treatment of orbital and ocular adnexal lymphoma is a reflection of the overall trend in management of non-Hodgkin lymphoma.\textsuperscript{1,16-18} This trend represents a departure from classic practice among ophthalmologists and oncologists, who have traditionally considered orbital radiotherapy the gold standard for treatment of orbital and ocular adnexal lymphoma.\textsuperscript{1,6,10,13} Several previous reports have focused on the efficacy and potential benefits of targeted immunotherapy.\textsuperscript{1,18}

The 5-year RFS for our cohort was 64.6%. This compares favorably with that reported in the literature.\textsuperscript{13} As expected, we found that RFS was higher in patients with primary orbital and ocular adnexal lymphoma than in those with secondary orbital and ocular adnexal lymphoma and that RFS was higher in patients with extranodal systemic disease than in those with nodal systemic disease. Our data also suggested a higher RFS for patients who have complete initial response to therapy.
compared with those who only achieved partial response. This highlights the importance of posttreatment imaging and also the recent role of positron emission tomography for assessment of response to treatment of orbital and ocular adnexal lymphoma.

On the basis of our data, we recommend a thorough staging workup, including a workup for systemic disease for all patients with primary or secondary orbital and ocular adnexal lymphoma. This staging workup should include total-body positron emission tomography, a bone marrow biopsy, and—for patients with some histologic subtypes of orbital and ocular adnexal lymphoma, such as MALT lymphoma and mantle cell lymphoma—gastrointestinal endoscopy. For most patients with orbital and ocular adnexal lymphoma, systemic targeted treatments, such as monoclonal antibody therapy or radioimmunotherapy, should be considered, because close to half of patients with primary orbital and ocular adnexal lymphoma at initial examination are found to have systemic involvement on careful staging. Even among the lowest risk histologic type of lymphoma (MALT), there was close to one-third incidence of non–stage IE disease at initial examination. The efficacy of targeted monoclonal antibody therapy for local control of orbital and ocular adnexal lymphoma needs to be compared with the efficacy of radiotherapy. In fact, the value of these treatment modalities for orbital and ocular adnexal lymphoma are currently being evaluated in prospective trials. Monoclonal antibody therapy may not only be as effective as orbital radiotherapy for local control of orbital and ocular adnexal lymphoma but also may offer better overall systemic control of lymphoma, as it is a systemic form of treatment. It may also be potentially less toxic to the orbital and ocular adnexal tissues compared with orbital radiotherapy.

Submitted for Publication: August 14, 2007; final revision received September 7, 2007; accepted September 8, 2007.

Correspondence: Bita Esmaeli, MD, Section of Ophthalmology, Unit 441, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030 (besmaei@mdanderson.org).

Financial Disclosure: None reported.

REFERENCES