Orbital Lymphomas: A Clinicopathologic Study of a Rare Disease

SHAHID AHMED, MD; RABIA K. SHAHID, MD; CRISTINA P. SISON, PHD; ALEXANDER FUCHS, MD; BHOOMI MEHROTRA, MD

ABSTRACT: *Objective:* To evaluate the clinicopathologic features and prognosis of patients with orbital lymphomas. *Methods:* Clinical and pathologic data of 35 patients with biopsy-proven orbital lymphoma diagnosed at a tertiary care hospital from 1992 to 2001 were reviewed. Lymphomas were divided into low-grade and high-grade lymphomas. Survival of patients was compared according to age, gender, disease site, extent of disease, tumor grade, and treatment modality by using log rank test. *Results:* Median patient age was 75 years (23-94) and the male-to-female ratio was 1:2.9. Twenty-three patients (66%) were diagnosed with low-grade lymphoma, and 12 patients (34%) were found to have high-grade lymphoma. Among low-grade lymphomas, marginal zone lymphoma (n = 6), follicle center cell lymphoma (n = 6), and small lymphocytic lymphoma (n = 5) were common entities, whereas diffuse large cell B-cell lymphoma (n = 5) was the most common entity in patients with high-grade lymphoma. Disease was clinically localized in 74% of patients at the time of diagnosis. Radiation alone or with chemotherapy was the primary treatment modality in 83% of patients. All except one patient had an objective response to therapy. Over the median follow-up period of 47 months (range, 1.5-141 months), disease recurred in 37% patients who achieved a complete response. The estimated 5- and 10-year survival rates were 64% and 42%, respectively. Overall, 13 (37%) patients died, 6 with high-grade and 7 with low-grade lymphoma. No clinical variable was found to be prognostically significant with respect to survival. *Conclusions:* Orbital lymphoma is a disease of the elderly with a female preponderance. It tends to be localized to the orbit at the time of diagnosis and responds well to local or systemic therapy. **KEY INDEXING TERMS:** Eye; Orbit; Lymphoma; Orbital lymphoma; Non-Hodgkin lymphoma; Marginal zone lymphoma; Diffuse large cell B cell lymphoma. **[Am J Med Sci 2006;331(2):79–83.]**

Orbital lymphoma is the most common malignant tumor of the eyes. It can occur either as the primary site of disease or rarely as a secondary site of systemic non-Hodgkin lymphoma (NHL) dissemination.[1–3] Although primary lymphoma of ocular adnexa involving orbit, conjunctiva, and eyelids accounted for 5% to 15% of all extranodal NHLs, overall it represents only 1% of all NHLs.[1–3]

Orbital lymphoma typically is a disease of the elderly.[1–3] It is localized to the orbit in a majority of patients at the time of presentation and may be difficult to differentiate from benign reactive lymphoid lesions.[3] With the recent advent of immunophenotype and molecular genetic methods, many new clinicopathologic entities have been identified among NHLs. Many cases of benign lymphoid reactive lesions of the eye that were previously described using the term *pseudolymphoma* in fact are found to have a clonal population of malignant cells.[4] Among different ocular adnexal lymphomas, extranodal marginal zone lymphoma (MZL) is the most common entity.[4–10]

We present here our experience with patients with orbital lymphoma. The aim of our study is to evaluate the clinicopathologic features of orbital lymphoma diagnosed over the past decade at our institution and to identify the prognostic variable that affects the survival of these patients.

Methods

The study protocol was approved by the hospital's Institutional Review Board. Medical records of 35 patients with biopsy-proven orbital lymphomas diagnosed at Long Island Jewish Medical Center, New York from 1992 to 2002 were reviewed. Cases of

From the Saskatoon Cancer Center, University of Saskatchewan, Saskatoon, Saskatchewan, Canada (SA); the Dow University of Health Sciences, Karachi, Pakistan (RKS); the Biostatistics Unit, North Shore-Long Island Jewish Research Institute, Manhasset, New York (CPS); and the Long Island Jewish Medical Center, New Hyde Park, New York (AF, BM).

Submitted for publication January 20, 2005; accepted for publication September 25, 2005.

Correspondence: Shahid Ahmed, MD, Clinical Assistant Professor, College of Medicine, Saskatoon Cancer Center, University of Saskatchewan, 20 Campus Drive, University of Saskatchewan Campus, Saskatoon, SK, Canada, S7N4H4 (E-mail: sahmed@scf.sk.ca).

Table 1. Characteristics of Patients with Orbital Lymphoma

Age, y (range)	75 (23–94)
M:F ratio	9:26
Localization, n (%)	
Orbit	22 (63)
Orbit with lacrimal gland involvement	5/22 (23)
Conjunctiva	14 (40)
Eyelid	1 (3)
Symptoms and signs, n (%)	
Visible tumor mass and/or eyelid swelling	12 (34)
Blurred vision and/or diplopia	11 (32)
Tearing and/or redness	11 (32)
Proptosis	6 (17)
Headache	1 (3)
Constitutional symptoms,[a] n (%)	1 (3)
Abnormal LDH, n/n (%)	4/25[b] (16)

[a] *Fever, night sweats, and >10% weights loss.*
[b] *LDH level at diagnosis was available in 25 patients.*

atypical lymphoid hyperplasia that did not have a confirmed monoclonal cell population were excluded. Of 35 cases of orbital lymphoma, pathologic slides from 26 cases were available and were reviewed by a pathologist (AF) and, based on morphology and immunophenotype, classified according to the World Health Organization classification.[11] Clinical staging was performed according to the Ann Arbor classification.[12] Complete staging work-up included computed tomographic scan of chest, abdomen and pelvis, gallium and/or positron emission tomographic scan, and bone marrow examination. Complete clinical response was defined as complete disappearance of the disease for a period of at least 1 month, whereas partial clinical response was defined as 50% or greater reduction in the measurable disease. For study purposes, all lymphomas were divided into two groups, "low-grade lymphoma" and "high-grade lymphoma". Low-grade lymphomas included extranodal MZL, follicle center cell lymphoma (FCL) (grade 1 and 2), small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), and lymphoplasmacytoid lymphoma. High-grade lymphoma included diffuse large cell B cell lymphoma (DLCL), mantle cell lymphoma, and FCL (grade 3). Survival was estimated from time of the diagnosis of lymphoma to death from any cause. Survival analysis was carried out using the Kaplan-Meier method. Comparison of survival curves according to age (≥65 versus <65), gender, disease site (orbit versus conjunctiva), extent of disease (localized versus systemic), tumor grade (low-grade versus high-grade), and treatment modality (radiation therapy versus other therapies) was done using the log-rank test.

Results

Clinical Features, Histopathology, and Staging of Orbital Lymphoma

The median age of patients with orbital lymphoma was 75 years (range, 23-94 y) and the male-to-female ratio was 9:26. Patients' characteristics are described in Table 1. Three patients had a remote history of NHLs and were in remission at the time of diagnosis. Nineteen (54%) patients had left eye involvement, 15 (43%) had right eye involvement, and 1 (3%) patient had bilateral disease. Vision abnormalities (31%), salmon-colored subconjunctival infiltrate (26%), visible mass (23%), proptosis (17%), eyelid swelling (17%), and tearing (11%) were common presenting signs and symptoms (Table 1). Some patients had more than one symptom. Median duration of symptoms prior to definitive diagnosis was 2.5 months (range, 0.5-13 mo). All lymphomas were of non-Hodgkin histologic type and of B cell origin. Twenty-three (66%) patients were diagnosed with low-grade lymphoma, and 12 (34%) patients were found to have high- grade lymphoma. Histopathology of the tumor is described in Table 2. Complete staging work was preformed in 21 (60%) patients, 14 patients with low-grade lymphoma and 7 patients with high-grade lymphoma. Of 21 patients, 14 (67%) had localized disease. Nine of 14 patients (64%) with low-grade lymphoma and five of seven (71%) with high-grade lymphoma had stage IE disease on complete staging work-up. Of the remaining 14 patients who had a limited staging work-up, 12 patients did not have evidence of systemic disease. Overall, 26 (74%) of 35 patients had localized disease at the time of diagnosis. One patient with SLL/CLL had peripheral blood involvement at the time of diagnosis. Lumber puncture was performed in seven patients (20%), two with low-grade and five with high-grade lymphomas. None had central nervous system (CNS) involvement at the time of diagnosis.

Table 2. Histopathology and Stage of the Disease in Patients with Orbital Lymphoma

Histopathology	All Patients, n	Stage 1, n	Stage 2, n	Stage 3, n	Stage 4, n	Staging not done, n
All lymphomas	35	14	0	3	4	14
Low-grade lymphomas	23	9	0	3	2	9
MZL	6	3	0	1	0	2
FCL (grade 1, 2)	6	3	0	0	0	3
SLL/CLL	5	2	0	1	2	0
Lymphoplasmacytoid	1	0	0	1	0	0
Unspecified low-grade lymphoma	5	1	0	0	0	4
High-grade lymphomas	12	5	0	0	2	5
DLCL	5	3	0	0	1	1
FCL (grade 3)	2	2	0	0	0	0
MCL	1	0	0	0	1	
Unspecified high- or intermediate- grade lymphoma	4	0	0	0	0	4

MCL, mantle cell lymphoma.

Table 3. Clinical Data of Patients with Most Common Lymphomas in the Present Study [a]

Type	Patients, n	Median age, y (range)	M:F Ratio	Radiation Therapy, %	Chemotherapy, %	Surgery, %	CR, %	Follow-up, mo (range)	Alive, %
DLBCL	5	67 (57–85)	3:2	80	60	40	60	63 (6–97)	40
MZL	6	56 (23–86)	2:4	83	0	17	80[b]	24 (8–36)	100
FCL	6	76 (70–84)	1:5	67	0	67	80[b]	71 (21–132)	67
SLL/CLL	5	72 (64–81)	1:4	40	40	20	40	23 (4–96)	60

[a] *Some patients were treated with combined modality of treatment.* [b] *Post-treatment data were not available in one patient.*
DLBCL, diffuse large B cell lymphoma.

Treatment, Response to Therapy, and Survival

All patients were treated and various therapeutic modalities were used. Many patients received more than one treatment. Of 23 patients with low-grade lymphoma, 16 patients (70%) received radiation therapy, 5 (22%) underwent surgical resection, and 2 (8%) had chemotherapy as the primary treatment modality. Of 12 patients with high-grade lymphoma, 9 patients (75%) were treated with radiation therapy (with or without chemotherapy), 2 (17%) with chemotherapy alone and 1 (8%) with surgery. The total radiation therapy dose ranged from 20 to 46 Gy with a median dose of 32 Gy. The most frequently used chemotherapy regimens were CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and CVP (cyclophosphamide, vincristine, and prednisone). CHOP was used mostly in patients with high-grade lymphomas.

Complete post-treatment follow-up data were available in 25 (71%) patients, 16 patients with low-grade lymphoma and 9 patients with high-grade lymphoma. Objective response was noted in all except one patient. Of 16 patients with low-grade lymphomas, 13 (81%) patients had complete response and 3 (19%) had partial response, whereas of nine patients with high-grade lymphoma, six (67%) had complete response, two (22%) had partial response, and one (11%) had disease progression. Median duration of follow up was 47 months (range, 1.5-141 mo). Disease recurrence was noted in 4 of 13 patients (31%) with low-grade and three of six patients (50%) with high-grade lymphoma who achieved a complete response to treatment. Two patients with stage 1 DLCL had CNS recurrence and died of progressive disease. In one patient, CNS recurrence was noted 33 months after completion of therapy and in the other patient the recurrence was noted 67 months after treatment completion. Clinical data of most prevalent lymphomas are described in Table 3.

Survival data of all 35 patients were available. Overall, 13 of 35 patients (37%) died during the follow-up period (Figure 1). The 5- and 10-year estimated survival was 64% and 42%, respectively. Seven of 23 patients (30%) with low-grade lymphoma and six of 12 patients (50%) with high-grade lymphoma died. Autopsy was performed in two patients. Overall, seven patients died of lymphoma (three patients with low-grade lymphoma and four patients with high-grade lymphoma) and four patients died of other illnesses. The cause of death was not known in two patients. Median survival in patients with high-grade lymphoma was 97 months, compared with 67 months in patients with low-grade lymphoma (P = NS) (Figure 2). Five- and 10-year estimated survival of patients with low-grade lymphomas was 58% and 46%, respectively, compared with 69% and 39% for patients with high-grade lymphomas. No significant difference was noted in the survival of patients according to gender, disease site, extent of disease, tumor grade, and treatment modality.

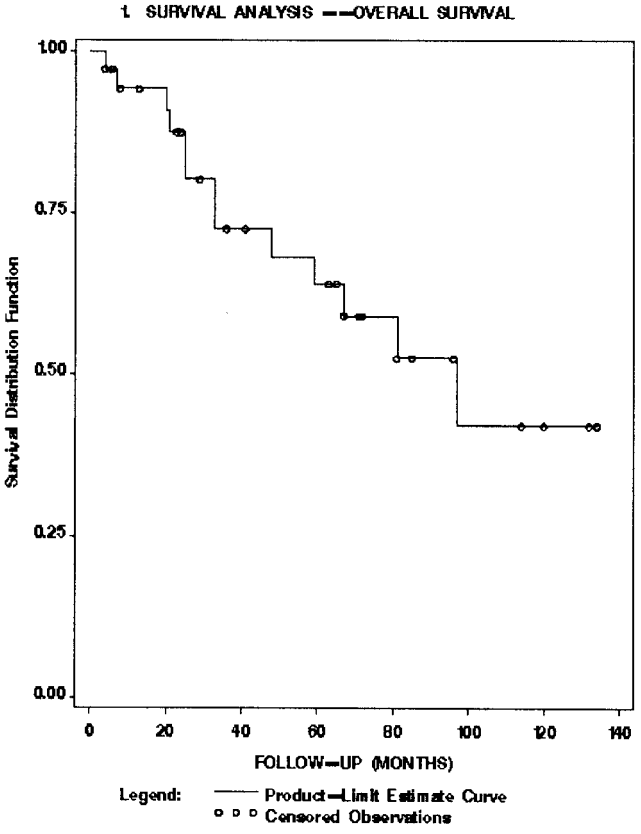

Figure 1. Survival curve of all patients with orbital lymphoma.

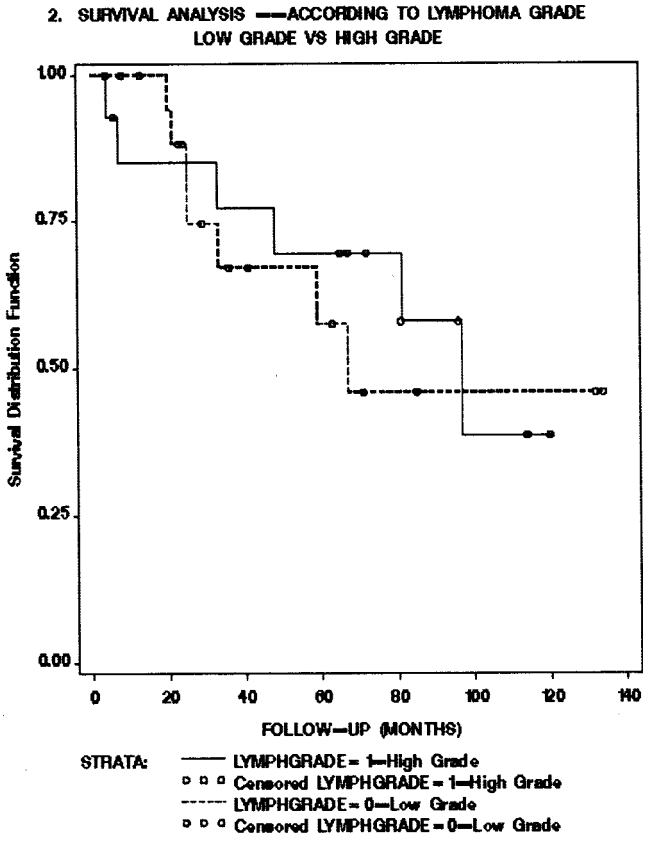

Figure 2. Survival curve of patients with low-grade or high-grade lymphoma.

Discussion

Similar to other series,[4–10] low-grade NHL was the most common lymphoma of the ocular adnexa in the present study. About two-thirds of cases were of low-grade and one-third of cases were of high-grade lymphoma. In agreement with previous observation,[4–10] MZL was the most common entity; however, FCL, SLL, and DLCL were also identified with almost equal frequency.

Although the age range varied from 23 to 94 years, the majority of patients with orbital lymphoma were elderly. Likewise, a female preponderance was noted in our series, in agreement with previous observation.[8,13] The disease was fairly evenly distributed between the two eyes, and bilateral involvement was rare. Despite the heterogeneous histopathology, the majority of lymphomas were localized to the orbit at the time of diagnosis. The orbit was the dominant site of the disease and was involved in about two-thirds of patients. The disease onset was insidious in many cases, especially in patients with low-grade tumor. Constitutional symptoms were rare, and the majority of patients had nonspecific local symptoms. Many patients were treated for a benign ophthalmic disorder prior to definitive diagnosis. The definitive diagnosis in these cases was obtained after several months of follow-up when persistent symptoms led to surgical biopsy.

Currently recommended therapy for stage IE tumors is radiotherapy, whereas disseminated disease is treated with chemotherapy. Local control with radiation therapy for orbital lymphoma has been excellent and in different series local control rates have ranged from 89% to 100%, with a distant metastases rate of 0% to 25%.[13–16] In our series, the response rate with all therapeutic modalities, either local or systemic, was high. Radiation therapy was the primary treatment modality in patients with low-grade lymphoma, whereas a large proportion of patients with high-grade lymphoma were treated with systemic chemotherapy in addition to local treatment. Radiation therapy was highly effective in our series. An objective response was noted in all cases treated with radiation, and most responses were complete. However, the disease recurred in seven patients who achieved a complete response to therapy. Of significance, two patients with DLCL had CNS recurrence and died of the disease. Long-term follow-up is, therefore, recommended in patients with orbital lymphoma who achieve a complete response to therapy.

Tumor grades, stage of the disease, and site of the tumor have previously been described as prognostic marker for survival.[4,13] In our series, we did not find any of these clinical variables to be prognostically significant. This may have been due to small sample size, few subjects per group, and relatively few events of death.

In summary, the present data confirm that orbital lymphoma is a disease of the elderly with a female preponderance. The majority of patients present with localized disease, and systemic symptoms are rare. Response to local or systemic therapy is excellent, but recurrence is common. Patients with high-grade lymphoma are at high risk of CNS recurrence. A longer follow-up period is required for patients with orbital lymphomas.

References

1. **Lambo MJ, Brady LW, Shields CL.** Lymphoid tumors of the orbit. In Alberti WE, Sagerman RH, editors. Radiotherapy of intraocular and orbital tumors. Berlin: Springer-Verlag 1993;205–16.
2. **Bairey O, Kremer I, Rakowsky E, et al.** Orbital and adnexal involvement in systemic non-Hodgkin's lymphoma. Cancer 1994;73:2395–9.
3. **Lauer SA.** Ocular adnexal lymphoid tumors. Curr Opin Ophthalmol 2000;11:361–6.
4. **Auw-Haedrich C, Coupland SE, Kapp A, et al.** Long term outcome of ocular adnexal lymphoma subtyped according to the REAL classification. Br J Ophthalmol 2001;85:63–9.
5. **White WL, Ferry JA, Harris NL, et al.** Ocular adnexal lymphoma: a clinicopathologic study with identification of lymphomas of mucosa-associated lymphoid tissue type. Ophthalmology 1995;102:1994–2006.

6. **Coupland SE, Krause L, Delecluse HJ, et al.** Lymphoproliferative lesions of ocular adnexa: analysis of 112 cases. Ophthalmology 1998;105:1430–41.
7. **Cahill M, Barnes C, Moriarty P, et al.** Ocular adnexal lymphoma-comparison of MALT lymphoma with other histological types. Br J Ophthalmol 1999;83:742–7.
8. **Fung CY, Tarbell NJ, Lucarelli MJ, et al.** Ocular adnexal lymphoma: clinical behavior of distinct World Health Organization classification subtypes. Int J Radiat Oncol Biol Phys 2003;57:1382–91.
9. **Hasegawa M, Kojima M, Shioya M, et al.** Treatment results of radiotherapy for malignant lymphoma of the orbit and histologic review according to the WHO classification. Int J Radiat Oncol Biol Phys 2003;57:172–6.
10. **Uno T, Isobe K, Shikama N, et al.** Radiotherapy for exteranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue originating in the ocular adnexa: a multiinstitutional retrospective review of 50 patients. Cancer 2003; 98:865–71.
11. **Jaffe ES, Harris NL, Stein H, editors.** WHO classification of tumors: pathology, genetics, tumors of haematopoietic and lymphoid tissue. Lyon: IARC Press; 2001.
12. **Smithers D.** Summary of papers delivered at the Conference on Staging in Hodgkin's disease (Ann Arbor). Cancer Res 1971;31:1869–70.
13. **Martinet S, Ozsahin M, Belkacemi Y, et al.** Outcome and prognostic factors in orbital lymphoma: a Rare Cancer Network study on 90 consecutive patients treated with radiotherapy. Int J Radiat Oncol Biol Phys 2003;55:892–8.
14. **Platanias LC, Putterman AM, Vijayakumar S, et al.** Treatment and prognosis of orbital non-Hodgkin's lymphomas. Am J Clin Oncol 1992;15:79–83.
15. **Smitt MC, Donaldson SS.** Radiotherapy is successful treatment for orbital lymphoma. Int J Radiat Oncol Biol Phys 1993;26:59–66.
16. **Bhatia S, Paulino AC, Buatti JM, et al.** Curative radiotherapy for primary orbital lymphoma. In J Radiat Oncol Biol Phys 2002;54:818–23.