Yonsei Medical Journal
Vol. 39, No. 3, pp. 196~201, 1998

Primary Lymphoma of the Eye

Jee Sook Hahn[1], Chang Ok Suh[2], Sang Yeul Lee[3], and Woo Ick Yang[4]

Lymphomas in the eye tend to be localized and to have a better prognosis. We reviewed the clinical presentation, treatment outcome and complications of primary lymphomas of the eye at a single institute focusing on the clinical significance of adequate staging and the prognostic value of pathological subtypes. Twenty-four patients with lymphoproliferative lesions of the eye were treated and followed up. The orbit was the most commonly involved site. Twenty-one patients had unilateral diseases and three patients had bilateral. Histological findings revealed 22 malignant lymphomas, one inflammatory pseudotumor and one atypical lymphoid hyperplasia. Using the NCI Working Formulation, most of the malignant lymphomas were primarily low grade: diffuse small lymphocytic, 15; diffuse small cleaved, three; diffuse large cell, three; and diffuse mixed, one. The stages of lymphoma were IAE in 21 patients, IBE in one patient, and IIAE in two patients. Twenty-five of the 27 treated eyes remained disease-free during the median follow-up period of 16 months. Nineteen patients received radiotherapy, five patients received chemo-radiotherapy and one patient received only surgical excision. Two patients relapsed outside the treated field. None of the patients complained of severe dry eye syndrome or cataract formation.

In conclusion, after complete staging work-up, locally-confined low grade orbital lymphomas can be up to 90% controlled with radiotherapy alone. By contrast, combined treatment is advised in patients with intermediate and high grade lesions.

Key Words: Orbital lymphoma, radiotherapy, low grade

Lymphoproliferative disorders of the eye can be grouped into four categories: reactive lymphoid hyperplasia (inflammatory pseudotumor), atypical lymphoid hyperplasia, intermediate lymphoid hyperplasia and malignant lymphoma (Knowles and Jakobiec, 1980). Primary lymphoma of the eye is the most common type among the rare primary tumors of the eye (Adams and Farr, 1981) and it has been estimated to account for 5~14% of extra-nodal non-Hodgkins lymphomas (Timothy *et al.* 1980). Most lymphomas of the eye are diffuse small lymphocytic type of non-Hodgkins lymphoma according to the NCI Working Formulation (Lazzarino *et al.* 1985; Reddy *et al.* 1988; Medeiros *et al.* 1989).

Diagnosis of the primary lymphoma of the eye can be made after exclusion of other site involvement, which means that systemic staging work-up is essential before final diagnosis and stage are made. Therefore, incomplete diagnosis and treatment without adequate staging work-up have raised some debate about the cure and systemic relapse rate in primary lymphoma of the eye (Jereb *et al.* 1984; Letschert *et al.* 1991; Keleti *et al.* 1992). The other reason which has troubled the proper treatment of these tumors is the difficulty in differentiating malignant lymphoma from benign reactive lymphoid hyper-

Received January 26, 1998
Accepted April 15, 1998
Departments of [1]Internal Medicine, [2]Radiation Oncology, [3]Ophthalmology, and [4]Pathology, Yonsei University College of Medicine, Seoul, Korea
Address reprint request to Dr. J.S. Hahn, Department of Internal Medicine, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea

plasia (Heersink *et al.* 1977; Chavis *et al.* 1978; Fuji *et al.* 1985; Medeiros *et al.* 1989).

We report here our experience of 24 patients with primary lymphoma of the eye focusing on the clinical significance of adequate staging and the prognostic value of pathological subtypes.

MATERIALS AND METHODS

Twenty-four patients with lymphoproliferative disease of the eye were evaluated and treated at Yonsei Medical Center between 1984 and 1997. Staging work-up included complete physical examination, blood count, serum chemistry and chest X-ray. An orbital computerized tomography (CT) scan was obtained routinely in all patients. CT was also performed in the abdomino-pelvis area in 19 patients, the chest in 15 and the brain in one. Whole body bone scan was done in 13 patients and gallium scan was done in 15. Bone marrow study was done in 15 patients.

We used the pathological criteria previously described (Knowles and Jacobiec, 1980) in order to differentiate four different categories of lymphoproliferative disorders of the eye. Histological diagnosis and classification of lymphoma were done according to the Working Formulation of non-Hodgkins lymphoma.

Radiotherapy was delivered by either linear accelerator or cobalt-60. We used the shield to save the cornea/lens and the contra-lateral eye. Nineteen patients were treated to a dose of 3,000 cGy or less in 180~200 cGy fractions while four patients were treated with more than 3,000 cGy. Complete response was defined as a complete disappearance of all clinical evidence of lymphoma by physical examination and/or orbital CT scan. Side effects were documented according to the patients' complaints and physical examination. Five patients with intermediate or high grade lymphomas were treated with combined chemotherapy; three patients with CHOP (cyclophosphamide, adriamycin, vincristine, prednisolone) and two patients with BACOP (bleomycin, adriamycin, cyclophosphamide, vincristine, prednisolone).

Overall survival was defined from the date of diagnosis to the last follow-up or to the time of death. Disease-free survival was defined from the time of complete response documentation to the last follow-up in a disease-free state. Median follow-up period for patients was 16 months (range; 2~92 months).

RESULTS

Of the 24 patients in the study, 15 were men and nine were women with a ratio of 1.7 : 1. The median age was 48 years (range, 13-71 years). The most common presenting complaints were those of a slowly growing mass of the eyelid and periorbital swelling (Table 1). Orbital lesion, which appeared in 12 patients, was the most commonly involved site at diagnosis. The other involved sites were: conjunctiva in six, eyelid in four, orbit and eyelid in one, and orbit and lacrimal gland in one. Three patients had bilateral diseases: two patients at the time of initial diagnosis (synchronous) and one patient with contra-lateral relapse (metachronous). A total of 27 sites, including relapsed sites, were treated. Histological findings at initial diagnosis revealed 22 malignant lymphomas, one inflammatory pseudotumor and one atypical lymphoid hyperplasia. Using the NCI Working Formulation, most of the malignant lymphomas were primarily low grade: diffuse small lymphocytic, 15; diffuse small cleaved, three; diffuse large cell, three; and diffuse mixed, one. Two patients of diffuse small lymphocytic lymphoma were previously diagnosed as inflammatory pseudotumor. Three other diffuse small

Table 1. Presenting signs and symptoms

Signs and symptoms	Number of patients
Visible mass	14
Periorbital swelling	9
Proptosis	7
Chemosis	6
Diplopia	5
Ptosis	4
Decreased visual field	2
Eye pain	2

Table 2. Clinical characterisitcs of 24 patients

Patients	Age/sex	Site	Symptom duration(months)	Bilaterality	Initial diagnosis	Histology	Stage	Radiotherapy dose(cGy)	Chemotherapy	Outcome	Follow-up (months)
1	M/71	lid	120	—	—	pseudolymphoma	IAE	3060	—	NED(expired)+	47
2	M/56	lid	4	—	—	low grade+++	IAE	2700	—	NED	2
3	M/70	lid	96	—	—	diffuse,small cleaved	IBE	3060	BACOP (1cycle)	NED	20
4	F/55	lid	36	—	—	diffuse,small cleaved	IAE	4600	—	NED*	92
5	M/21	conjunctiva	12	—	—	atypical lymphoid hyperplasia	IAE	2600	—	NED	30
6	F/44	conjunctiva	5	—	—	low grade	IAE	3060	—	NED	10
7	F/48	conjunctiva	4	—		low grade	IAE	3060	—	NED	15
8	F/54	conjunctiva	48	—	conjunctivitis	low grade	IAE	3000	—	NED	16
9	F/60	conjunctiva	10	—	NSI***	low grade	IAE	3060	—	NED	14
10	M/44	conjunctiva	12	—	—	diffuse small, cleaved	IAE	3000	CHOP (2 cycles)	NED	27
11	M/35	orbit	8	—	—	low grade	IAE	2520	—	NED	12
12	M/38	orbit	2	—		low grade	IAE	3060	—	NED	14
13	M/39	orbit	15	—		low grade	IAE	3060	—	NED	5
14	M/47	orbit	3	—		low grade	IAE	2700	—	NED	18
15	M/59	orbit	24	—	NSI***	low grade	IAE	3000	—	NED	18
16	M/50	orbit	60	+	pseudolymphoma	low grade	IIAE	2000(both)	—	NED	12
17	F/48	orbit	24	—	pseudolymphoma	low grade	IAE	2600	—	NED	16
18	F/46	orbit	24	—	—	low grade	IAE	2520	—	NED	25
19	F/57	orbit	60	—	—	low grade	IAE	—	—	NED	42
20	M/13	orbit	6	—	pseudolymphoma	diffuse large	IAE	3600	CHOP (1 cycle)	NED	71
21	M/24	orbit	2	—	—	diffuse large	IAE	3000	BACOP (6 cycles)	NED	35
22	M/38	orbit	2	—	—	diffuse mixed	IAE	5000	—	expired++	5
23	F/70	orbit,lid	3	+	—	low grade	IIAE	2520(both)	—	NED	3
24	M/30	orbit** lacrimal gland	5	+**	hemangioendothelioma	diffuse large	IAE	3960** (2 cycles)	CHOP**	expired++	16

*: Chest wall relapse, **: relapse after surgery(exenteration), NED: no evidence of disease, ***: non-specific inflammation, +: cerebrovascular accident, ++: progression, +++: MALTOMA

lymphocytic patients were previously diagnosed as non-specific inflammation in two and as allergic conjunctivitis in one. Two of the patients with diffuse large cell type were previously diagnosed as hemangioendothelioma and inflammatory pseudotumor, respectively. The final clinical stage of lymphoma was IAE in 21 patients, IBE in one patient and IIAE in two patients.

Radiotherapy was uniformly well tolerated in all patients. Nine patients experienced mild conjunctival swelling and erythema and two patients complained of epiphora. None of the patients were diagnosed as having a radiotherapy-induced complication such as severe dry-eye syndrome or cataract formation up to the time of the last follow-up. Pertinent patient data are presented in Table 2.

Fourteen low grade lymphoma patients, one diffuse small cleaved type, one inflammatory pseudotumor and one atypical lymphoid hyperplasia with stage I-II after complete staging work-up showed a complete response after radiotherpy. They remained in a disease-free state except the patient with inflammatory pseudotumor who died from cerebrovascular hemorrhage without any evidence of tumor recurrence. One patient with stage IAE, diffuse small cleaved type and one patient with stage IAE, diffuse large cell type after complete staging work-up were unresponsive to two cycles and one cycle, respectively, of systemic chemotherapy (CHOP). These refractory lesions to chemotherapy responded completely to additional radiotherapy. One patient with stage IAE, diffuse large cell lymphoma is in a disease-free state after combined chemo-radiotherapy (BACOP 6 cycles). One patient with stage IBE showed a partial response after one cycle of BACOP chemotherapy. He was averse to chemotherapy. However, additional radiotherapy induced a complete response in this patient. One patient with low grade, stage IAE refused any treatment after complete excision of the primary mass. She remains in a disease-free state. Two patients who had a lymphoma confined to the orbit relapsed outside the radiotherapy field (distant relapse). One patient with diffuse small cleaved type relapsed in the chest wall, which was controlled with 3,600 cGy of radiotherapy. The other patient with a diffuse large cell type relapsed in the contra-lateral orbit, which progressed to a systemic disease. This patient died following combined radiotherapy and two cycles of chemotherapy (CHOP). Another patient with a diffuse mixed cell type responded partially to radiotherapy with a dosage of 5,000 cGy, but this patient also died from systemic progression after radiotherapy. The staging work-up for these two expired patients was incomplete. CT scan was performed only in the orbital lesions in both patients. Twenty-five of 27 treated eyes (92.5%) remained in a disease-free state with a 5-year survival rate of 89% (Fig. 1).

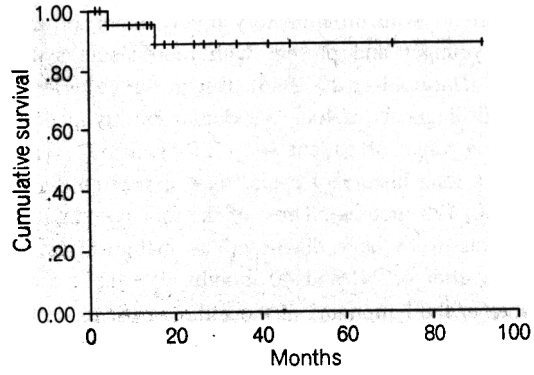

Fig. 1. Overall survival of all patients

DISCUSSION

Lymphoma of the orbit and ocular adnexa are rare. Less than 10 percent of patients with lymphoma present with the eye as a primary site (Timothy *et al.* 1980; Fitzpatrick and Macko, 1984). The median age of patients with primary lymphoma of the eye is generally in the sixth decade, while it was 48 years in our study. But a wide range of patient age exists in reported cases as well as in our patients (range 13-71 years). The presenting clinical manifestations are mass, proptosis, chemosis and orbital swelling based on the primary lesions in the eye structure. The development of symptoms in these patients is characterized by a chronic, progressive course. Therefore, a biopsy is required to establish the diagnosis of the primary lymphoma of the eye. When required, a surface immunologic marker study facilitates the diagnosis.

Patients with inflammatory pseudotumor are usually younger and present with more acute symptoms (Barthold *et al.* 1986). But in our experience, initial diagnosis of four pseudotumors was made in a wide range of patient age (13, 48, 50, 71 years) with a long history of eyelid mass and proptosis (6, 24, 60, 120 months). Three of the four pseudotumor patients were later diagnosed as malignant lymphoma after 4, 24, and 40 months. We don't know whether the lymphoma of those three patients developed from pseudotumors or whether the previous diagnoses were inaccurate. However, there seems to be a possibility of transition from inflammatory pseudotumor into lymphoma. Another three patients with diffuse small lymphocytic type had been previously diagnosed as a nonspecific inflammation or a conjunctivitis after biopsy. Since the previous biopsy slides were unavailable, we could not confirm in these three patients whether their previous lesions were the early stages of lymphoproliferative lesions or simple inflammatory lesions. Therefore, based on our experience, chronic inflammatory changes in the eye lesion need to be closely monitored for transformation into malignant lymphoma.

Any area of the orbit and adnexa may be affected by lymphoma, and up to one-quarter of patients with primary lymphoma of the eye present with bilateral disease (Keleti *et al.* 1992). In our experience, one patient (5%) developed lymphomatous involvement of the non-irradiated contra-lateral eye. Therefore, it is quite important to examine both eyes at the initial diagnosis as well as during follow-up examinations. In general, clinical features such as unilaterality or bilaterality of the primary lymphoma of the eye do not correlate with the outcome (Smitt and Donaldson, 1993).

According to the criteria of Knowles and Jacobiec (Keleti *et al.* 1992), lymphoid lesions of the eye are classified histologically as benign, indeterminate and malignant. Atypical lymphoid hyperplasia and indeterminate lesions are often monoclonal and have had the same clinical course as low grade lymphoma (Bessell *et al.* 1988; Medeiros *et al.* 1989). About 0-30% of polyclonal infiltrates may also develop into lymphoma (Knowles and Jakobiec, 1980; Medeiros *et al.* 1989). The majority of malignant lymphomas of the eye are low grade, particularly in conjunctival lesions. In contrast to this, diffuse large cell lymphoma is primarily seen in the orbit and usually involves the adjacent sinus and structures. In our series, three patients had diffuse large cell type occurring in the orbit (two patients) and in the lacrimal gland (one patient).

Pathological subtype by the NCI Working Formulation is the most consistently important factor in localized lymphoma in predicting prognosis. Inflammatory pseudotumor has been treated with radiotherapy and showed an excellent prognosis. Platanias et al. also suggested that low grade small lymphocytic lymphoma with localized disease can be more easily controlled with radiotherapy alone than by surgical excision (Platanias *et al.* 1992). This is because surgical excision alone may result in significant cosmetic and/or functional defects, and it is frequently accompanied by recurrence, as with one of our patients with diffuse large cell type. In our series, all the patients with low grade localized lesions after complete staging work-up were cured with radiotherapy alone.

Chao *et al.* suggested that the primary lymphoma of the eye should be diagnosed for those patients who have undergone vigorous staging work-up including orbital, thoracic and abdominal CT scan (Chao *et al.* 1995). But Platanias *et al.* suggested that orbital CT scan and bone marrow study are enough (Platanias *et al.* 1992). In a review of the literature, less than 20% of patients tended to have a systemic dissemination after complete staging work-up, as Chao *et al.* reported (Chao *et al.* 1995). This is an important issue in reducing the high incidence of systemic progression of the disease after successful local control with radiotherapy alone. High systemic relapses were reported after radiotherapy alone in the era before CT scans were commonly utilized in staging work-up (Kim and Fayos, 1976; Knowles and Jakobiec, 1980; Fitzpatrick and Macko, 1984). In the current study, two patients who were evaluated with orbital CT scan alone progressed to a systemic disease after local radiotherapy. One possible explanation of this systemic progression is the incomplete and inaccurate staging work-up.

The issue of whether bulky disease deserves a higher dosage of radiotherapy is controversial. Usually 3,000 cGy is suggested as a sufficient dosage

for local control with acceptable morbidity for low grade as well as intermediate grade of diffuse small cleaved cell lymphoma. Smitt and Donaldson suggested 3,600~4,000 cGy for high grade lesions (Smitt and Donaldson, 1993). Most patients in our study were treated to a dose of 3,000 cGy or less in 180~200 cGy fractions. Diffuse mixed and large cell types were treated with somewhat higher dosages (Table 2). In the dose range used in our patients, severe complications, such as cataract formation were not found after the completion of radiotherapy with lens protection techniques.

Chemotherapy is generally reserved for patients with intermediate or high grade lesions or for low grade patients with systemic symptoms, because a 40% to 60% systemic relapse rate has been observed in higher grade (intermediate/high grade) lymphomas (Bessell *et al.* 1988). Diffuse large cell lymphomas have usually been associated with aggressive behavior or with higher stages indicating this subtype should be treated by combined chemoradiotherapy. In our study, two patients with diffuse small cleaved lymphocytic type and two patients with diffuse large cell type were cured with combined chemoradiotherapy while one patient with diffuse large cell type progressed to a systemic disease and died even with chemotherapy after systemic progression.

In conclusion, an overall 90% cure rate with radiotherapy alone can be expected with acceptable morbidity in locally confined, low grade, primary lymphoma of the eye. It is suggested that other intermediate and high grade lesions be treated with combined chemoradiotherapy after complete staging work-up.

ACKNOWLEDGEMENTS

We thank Mr. Bob Ross for his editorial assistance in English.

REFERENCES

Adams YG, Farr HW: Primary orbital tumors. *Am J Surg 122: 726-731, 1981*

Barthold HJ, Harvey A, Markoe AM, Brady LW, Augsburger JJ, Shields JA: Treatment of orbital pseudotumors and lymphoma. *Am J Clin Oncol 9: 527-532, 1986*

Bessell E, Henk J, Whitelocke A: Orbital and conjunctival lymphoma treatment and prognosis. *Radiother Oncol 13: 237-244, 1988*

Chao CKS, Kin HS, Devineni VR, Smith M: Radiation therapy for primary orbital lymphoma. *Int J Radiat Oncol Biol Phys 31: 929-934, 1995*

Chavis RM, Garner A, Wright JE: Inflammatory orbital pseudotumor, a clinicopathological study. *Arch Ophthalmol 96: 1817-1822, 1978*

Fizpatrick P, Macko S: Lymphoreticular tumors of the orbit. *Int J Radiat Oncol Biol Phys 10: 333-340, 1984*

Fuji H, Fujisada H, Kondo T, Takahashi T, Okada S: Orbital pseudotumor; histopathological classification and treatment. *Ophthalmology 190: 230-242, 1985*

Heersink B, Rodrigues MR, Flanagan JC: Inflammatory pseudotumor of the orbit. *Ann Ophthalmol 9: 17-19, 1977*

Jereb B, Lee H, Jakobiec FA, Kutcher J: Radiation therapy of conjunctival and orbital lymphoid tumors. *Int J Radiat Oncol Biol Phys 10: 1013-1019, 1984*

Keleti D, Flickinger JC, Hobsson SR, Mittal BB: Radiotherapy of lymphoproliferative diseases of the orbit. *Am J Clin Oncol 15: 422-427, 1992*

Kim YH, Fayos JV: Primary orbital lymphoma; a radiotherapeutic experience. *Int J Radiat Oncol Biol Phys 1: 1099-1105, 1976*

Knowles D, Jakobiec F: Orbital lymphoid neoplasms. A clinicopathological study of 60 patients. *Cancer 46: 576-589, 1980*

Lazzarino M, Morra E, Rossa R: Clinicopathologic and immunologic characteristics of non-Hodgkins lymphomas presenting in the orbit. *Cancer 55: 1907-1912, 1985*

Letschert JGL, Gonzalez DG, Oskam J, Korneef L, van Dijk JDP, Boukes R, Bras J, van Heerde P, bartelink H: Results of radiotherapy in patients with stage I orbital non-Hodgkins lymphoma. *Radiother Oncol 22: 36-44, 1991*

Medeiros LJ, Harmon DC, Linggood RM, Harris NL: Immunohistologic features predict clinical behavior of orbital and conjunctival lymphoid infiltrates. *Blood 74: 2121-2129, 1989*

Platanias LC, Putterman AM, Vijayakumar S, Recant W, Weicchselbaum RR, Bitran JD: Treatment and prognosis of orbital non-Hodgkins lymphomas. *Am J Clin Oncol 15: 79-83, 1992*

Reddy EK, Bhatia P, Evans RG: Primary orbital lymphomas. *Int J Radiat Oncol Biol Phys 15:1239-1241, 1988*

Smitt M and Donaldson SS: Radiotherapy is a successful treatment for orbital lymphoma. *Int J Radiat Oncol Biol Phys 29: 59-66, 1993*

Timothy AR, Lister TA, Katz D, Jones AE: Localized non-Hodgkins lymphoma. *Eur J Cancer 16: 799-807, 1980*