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Prognosis for Patients in a Korean Population with Ocular Adnexal Lymphoproliferative Lesions

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Purpose: To analyze the clinical features, treatment outcomes, and prognostic factors associated with lymphoproliferative lesions of the ocular adnexa in a Korean population.

Methods: Data from 69 patients treated for adnexal lymphoproliferative disease in the 12-year period from 1991 to 2002 were retrospectively evaluated.

Results: The 69 patients had a median age of 46 years (range, 15–73 years); 60 of these patients were diagnosed with extranodal marginal zone B cell lymphomas (MALT lymphomas) and had 10 year cause specific survival and relapse free survival rates of 95.6% and 82.6%, respectively. Of 6 patients (8.7%) with concurrent systemic lymphoma, including 4 diagnosed with stage IV disease, 3 died from lymphoma. Only one patient with a primary ocular adnexal MALT lymphoma developed systemic lymphoma, which was treated with surgical resection. Local recurrence either at the primary site or in the fellow eye occurred in 11.6% of patients at a median follow-up time of 102 months (range, 79–132 months), and was controlled using repeat irradiation in all cases. Statistical analysis showed the presence of concurrent systemic lymphoma, bilateral disease, and an advanced stage at diagnosis, were linked to lymphoma-related death (Log-rank test, $p < 0.05$) and systemic progression (Fisher's exact test, $p < 0.05$), and that the tumor location was not a prognostic factor for lymphoma-related death or relapse at any site.

Conclusions: Ocular adnexal lymphoproliferative disease in Koreans occurred at a relatively young age, and was mostly orbitally located and of the MALT subtype, which is highly localized and rarely associated with extraorbital relapse. Primary or secondary status, stage at presentation, and bilaterality were found to be prognostic factors.

Malignant lymphomas forming in the ocular adnexa account for 8% of all extranodal non-Hodgkin lymphomas. A confirmed malignant lymphoma has a high rate of extraorbital spread over 5 years (60%)[1] and the higher the lymphoma grade, the higher the potential for spread.[2,3]

Previous studies suggest that extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT lymphomas) constitute a higher proportion of primary ocular adnexal lymphomas in Korea (86–98%) compared with Western countries (50–78%).[3–7] MALT lymphomas are characterized by localized disease and rarely spread systemically.[4,5,8] However, several reports indicate approximately one-third of MALT lymphoma patients present at diagnosis with disseminated disease, although the survival in such patients appears to be the same as that for patients with localized disease.[9]

As with malignant ocular adnexal lymphomas, many prognostic studies for MALT lymphomas have been performed and have identified associations with histology type, clinical stage, primary location, and bilaterality at presentation.[2,10–14] Many reported ocular adnexal lymphoma clinical characteristics differ between Korea and Western countries, especially in terms of incidence and prognosis. There remains insufficient information regarding factors that influence the probability of successful tumor control in ocular adnexal lymphomas.

The present retrospective study assessed clinical features and treatment outcomes in ocular adnexal lymphoproliferative disease patients classified according to the World Heath Organization (WHO) modification of the Revised European-American Classification of Lymphoid neoplasm (REAL) classification, and analyzed the impact of clinical characteristics and other variables on prognosis.

METHODS

In the 12-year period from 1991 to 2002, 69 patients (77 eyes) with ocular adnexal lymphoproliferative disease were evaluated and treated in the Department of Ophthalmology, Yonsei University College of Medicine. Information collected from medical records included patient age, gender, medical

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history, time to diagnosis from onset of symptoms, presenting complaint, duration of symptoms, primary tumor site, systemic involvement, pathology reports, stage at diagnosis, treatment modality, complications, recurrence, and survival.

Provisional diagnosis of lymphoproliferative disease was made on the basis of routine histology and immunohistochemistry for B and T cells. Molecular assessment using the polymerase chain reaction technique for the immunoglobulin heavy light chain gene and T-cell receptor gamma chain gene rearrangements was incorporated in the final diagnosis. All cases were reexamined and reclassified according to WHO classification by a hematopathologist.

The location and extent of tumors was determined clinically and radiologically. Orbital lesions had predominantly postseptal involvement, and were subdivided in lesions arising from the lacrimal gland and non-lacrimal gland. A lacrimal gland lesion was defined as a lesion centered on the lacrimal gland even when adjacent tissues were involved. A distinct subcutaneous mass in the preseptal area was defined as an eyelid lesion. Conjunctival lesions had movable, salmon-pink conjunctival infiltrates without adjacent eyelid or orbit involvement.

All patients underwent clinical and laboratory evaluation and were staged according to the Ann Arbor system. Laboratory tests were performed at the Hematology-Oncology Department for pretreatment staging evaluation. These included complete blood count (CBC), erythrocyte sedimentation rate (ESR), liver function, lactate dehydrogenase (LDH), and β2-microglobulin assays, as well as CT scans (head and neck, chest, abdomen, and pelvis), whole body bone scans, and bone marrow biopsies. Where necessary, orbital CT was performed to detect any changes in tumor size at follow-up. Patients with simultaneous bilateral lesions without involvement of any other site outside the adnexa were classified as stage IE disease. No patients had autoimmune disease.

Six of the 77 lesions (3 conjunctival MALT lymphomas, 3 reactive lymphoid hyperplasias) underwent observation only, without treatment, as they were asymptomatic and minimal (Table 1, www.op-rs.com, Article Plus). Patients with a concurrent systemic MALT lymphoma at diagnosis and high grade lymphoma such as a diffuse large B cell lymphoma or an NK/T cell lymphoma received multiagent CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy with additional RT for local lesions. RT dose ranged from 5.4 Gy to 30.6 Gy (median, 30.6 Gy) in a fraction size of 1.8 Gy to 2.0 Gy.

Complete response (CR) was defined as the complete disappearance of all clinical evidence of lymphoma according to physical examination and orbital CT. Patients were followed every month until CR was declared. After the lesion had resolved, patients were followed every 6 months to identify any recurrence or systemic progression (SP).

SPSS (Chicago, IL, U.S.A.) software was used to assess the association between clinical parameters (age, gender, tumor site, primary or secondary status, bilaterality, and stage at diagnosis) and the variables of lymphoma related death, relapse at any site, and SP. Cause-specific survival (CSS) and relapse-free survival (RFS) were determined using the Kaplan-Meier method. Univariate analysis used log-rank tests to determine associations between individual clinical features and CSS and RFS. The association between the proportion of SP patients and individual clinical characteristics was analyzed using Fisher's exact test for 2 by k tables.

RESULTS

Clinical and Pathologic Features. The study involved 69 patients with 77 ocular adnexal lymphoproliferative lesions. The population comprised 40 males and 29 females with a median age at diagnosis of 46 years and a mean follow-up period of 74 months (range, 6–168 months). Eight (12%) patients had bilateral disease at presentation, and the number of bilateral patients increased to 13 (18.8%) over the follow-up period (Table 1, www.op-rs.com, Article Plus).

Proptosis was the major orbital lesion symptom, and a salmon pink-like mass on the subconjunctiva was the most common complaint in cases of conjunctival lesions (Table 2, www.op-rs.com, Article Plus).

Table 3 (www.op-rs.com, Article Plus) shows the locations and histologic subtypes according to the WHO classification. Excluding the 6 reactive lymphoid hyperplasia patients, of the remaining 63 patients, 60 (95.2%) had malignant lymphomas of the MALT subtype. As for other histologic types, 2 patients had tumors classified as diffuse large B-cell lymphomas, and 1 patient had a bilateral extranodal NK/T cell lymphoma originating from the ethmoid sinus.

Treatment Outcomes. Sixty-three of the 71 treated lesions (88.7%) showed CR following initial treatment. The remaining 8 lesions (11%)— 4 eyes with orbital MALT lymphomas, 2 eyes with conjunctival MALT lymphomas, and 2 eyes with orbital NK/T cell lymphomas—showed a partial response with gradual regression of the local lesions.

Systemic Invasion. Only 6 patients (8.7%) presented with concurrent systemic lymphoma (secondary lymphoma) at diagnosis, comprising 5 MALT lymphomas and 1 NK/T cell lymphoma (Table 4, www.op-rs.com, Article Plus). Three of these 6 patients were successfully treated according to final follow-up examinations. The first patient had a MALT lymphoma in the forehead (confirmed by excisional biopsy) and underwent 30 Gy RT, which resulted in CR and showed no recurrence at 96 months after treatment. The second patient had a MALT lymphoma in the lacrimal gland, which resolved over the 96 months from diagnosis, and mediastinum lymph node enlargement (detected by chest CT at presentation). However, this patient had a local tumor relapse in the inferior rectus muscle of the fellow eye at 24 months after treatment. The third patient had a single-mass MALT lymphoma lesion in the chest wall, and showed CR without recurrence at 80 months after treatment. The other 3 patients (2 MALT lymphomas, 1 extranodal NK/T cell lymphoma) showed SP and were found to have systemic dissemination at diagnosis, which led to lymphoma-related deaths. Two MALT lymphomas were less aggressive (resulting in death after 48 and 42 months of treatment) than the extranodal NK/T cell lymphoma, resulting in death due to multiple thoracoabdominal lymph node involvement and lung and liver metastasis after 3 months of intensive combined chemotherapy and RT. For a month, intravenous and oral steroids were given to the latter patient due to a diagnosis of an inflammatory pseudotumor.

Only 1 of 60 primary ocular adnexal lesions showed SP, this being a subcutaneous nodule on the right shoulder, which pathology confirmed as a MALT lymphoma at 12 months after RT for bilateral lacrimal gland MALT lymphoma. The tumor was surgically resected and there was no recurrence at any site over the 108 month follow-up (Table 4, www.op-rs.com, Article Plus).

Survival. There were 3 lymphoma related deaths, and 5 deaths overall, during the study period. The 10-year CSS, overall survival (OS), and RFS rates were 95.6%, 92.8%, and 82.6%, respectively (Fig. 1, www.op-rs.com, Article Plus). Three patients developed unrelated systemic malignancies, namely hepatoma (n = 1), lung cancer (n = 1), and renal cell cancer (n = 1). The hepatoma patient died at 13 months after RT for orbital lymphoma. The lung cancer patient was diagnosed at 18 months after RT for orbital lymphoma and remains alive without orbital lymphoma or lung cancer relapse at 85 months after treatment for orbital lymphoma. The renal cell carcinoma was diagnosed incidentally following abdomino-pelvic CT in a patient who underwent a nephrectomy before radiation for orbital lymphoma. That patient remains alive without renal cell cancer at 108 months, but had a local lymphoma relapse in the inferotemporal orbit of the fellow eye at 93 months after diagnosis. Another patient died of intercurrent disease at 102 months after radiation for orbital lymphoma.

Local Relapse. Local tumor relapse at the primary site or in the fellow eye occurred in 8 (11.6%) patients over a median 102 months follow-up (range, 79–132 months) (Table 5, www.op-rs.com, Article Plus). Local relapse at the primary site occurred in 5 patients at a median time of 58 months (range, 36–60 months) from complete remission to recurrence, and in the fellow eye in 5 patients at a median time of 58 months (range, 6–120 months).

Analysis of Prognostic Factors. Age, gender, and tumor location were found to be not associated with CSS, RFS, or SP (Table 6, www.op-rs.com, Article Plus). In contrast, primary or secondary tumor status was associated with CSS (log-rank test, $p = 0.011$) (Fig. 2A, www.op-rs.com, Article Plus) and SP (Fisher's exact test, $p = 0.002$), with no primary lymphoma patients dying from disease compared with 50% of secondary lymphoma patients. In addition, only 1.6% of primary lymphoma patients showed SP, compared with 50% of secondary lymphoma patients. Bilaterality at presentation was associated with CSS (log-rank test, $p = 0.004$) (Fig. 2B, www.op-rs.com, Article Plus) and SP (Fisher's exact test, $p = 0.004$), with only 1.6% of patients with unilateral disease at presentation dying from disease, compared with 25% of bilateral disease patients. In addition, only 1.6% of these unilateral disease patients showed SP, compared with 37.5% of bilateral disease patients. Stage at diagnosis was also associated with CSS (log-rank test, $p < 0.001$) (Fig. 2C, www.op-rs.com, Article Plus) and SP (Fisher's exact test, $p < 0.001$), with no stage 1 or stage 2 patients dying of lymphoma, compared with 75% of stage 3 or stage 4 patients. In addition, only 1.7% of stage 1 or stage 2 patients showed SP, compared with 75% of stage 3 or stage 4 patients.

Site of Occurrence. Clinical features and treatment outcomes were analyzed according to the site of adnexal involvement (Table 7, www.op-rs.com, Article Plus). Although the statistical analysis showed that conjunctival lesion patients did not differ from non-conjunctival lesion patients in terms of CSS, RFS, and SP, no conjunctival lesion patients died from disease or showed SP during follow-up. Lacrimal gland patients also showed no lymphoma related deaths, with only one case of mediastinal lymph node enlargement at diagnosis, which spontaneously regressed without treatment. The one bilateral eyelid MALT lymphoma case showed CR in the local adnexal lesion after combined chemotherapy and RT. Initially, the patient presented with bilateral upper nasal eyelid swelling with orbital infiltration according to CT, and palpable multiple bilateral neck nodes, which open biopsy and pathology confirmed as a MALT lymphoma. Abdominopelvic CT revealed an enlargement of the paraaortic and pelvic lymph nodes, Systemically, multiple neck nodes and the paraaortic node showed partial response at 11 months after treatment. However, the patient died due to bone marrow and bilateral inguinal lymph node involvement at 42 months after treatment.

A list of RT complications is shown in Table 8 (www.op-rs.com, Article Plus). The most frequent complaint was dry eyes (20.6%), while visual loss due to cataracts occurred in three patients at 39, 56, and 67 months after RT, and was corrected by cataract extraction. No patients were diagnosed with radiation retinopathy. Of five patients with tearing, one was diagnosed with a common canalicular stenosis at 48 months after RT for a lacrimal sac lymphoma, and this patient underwent a conjunctivo dacryocystorhinostomy.

DISCUSSION

In the present study, MALT lymphomas constituted 95.2% of all malignant ocular adnexal lymphomas. This finding is consistent with those reported in other studies of Asian populations.[5,15–17] The present findings also concur with those of others showing that follicular lymphoma and chronic lymphocytic lymphoma or leukemia are rare in Asian countries, including Korea.[5,18] Indeed, follicular lymphoma was not diagnosed in the present study, while studies of Western populations report follicular lymphoma is the second most common subtype.[6,19] A high MALT lymphoma frequency in the current and previous studies suggests extranodal predominance might be a characteristic of malignant lymphomas in Korea. Such findings might be related to the high prevalence of Helicobacter pylori infection in Korea.[20]

Most previous studies generally report MALT lymphomas in patients from 57 to 66 years old,[1–3,6,10,12–14] yet patients in the present series had a mean age of 46 years, consistent with previous reports indicating that there might be a higher incidence of MALT lymphoma among younger Koreans than previously recognized.[4,5]

The relationship between malignant lymphoma incidence and ocular adnexa location remains a topic of debate. The present series found that 63.8% of malignant

lymphomas were orbitally located, about twice as common as those located in the conjunctiva (34.8%), consistent with the findings of others.[1] The high incidence of orbital lymphoma in the present study would explain the major symptom being proptosis, which is interesting considering that orbital soft tissue has less intrinsic lymphoid tissue than the conjunctiva.[21]

MALT lymphoma is known to progress slower than non-MALT lymphoma, and is very responsive to primary therapy, either radiation or chemotherapy. In addition, a previous Korean study reported that ocular adnexal MALT lymphomas were associated with a higher survival rate (98%) than stomach MALT lymphomas (84%).[22] Most Asian studies of MALT type ocular adnexal lymphomas report CSS being over 90%.[4,5] The present analysis of 60 MALT lymphoma patients found a lower frequency of advanced stage lymphomas (5%) at diagnosis compared with frequencies ranging from 18% to 37% in Western studies.[9,12,23–24] However, our analysis showed that advanced stage MALT lymphomas at diagnosis may have a more aggressive course and a higher mortality rate than localized disease. Two of three patients (67%) with MALT lymphoma dissemination at diagnosis died from systemic progression at 42 months and 48 months after treatment. Fischer et al. suggested that MALT lymphoma after dissemination is not a favorable subcategory of low grade disease, showing only a median failure free survival period of 2.3 years and an overall 10 year survival of 21% in advanced stage patients treated with combination chemotherapy.[25] However, other authors found that MALT lymphoma patient outcomes were not affected by dissemination, reporting estimated 10 year OS rates of 86% and 80% for localized and dissemination groups, respectively.[9]

In the current study, 5 MALT lymphomas (8.3%) exhibited in-field recurrence in the ocular adnexa, and all of them were easily cured by repeated RT. Le et al. reported freedom from local relapse or local control was 100% after RT.[26] Uno et al.[14] found that only 3 of 50 patients (6%) exhibited in-field recurrence in the ocular adnexa, and Martinet et al.[13] reported only 1 of 90 primary orbital lymphomas (1%) exhibited local relapse at 11 months after radiation. In contrast, Raderer et al. reported a high local relapse rate of 33.3% (4 of 12 patients) in ocular adnexa MALT lymphoma patients.[27] However, most recurring tumors in the ocular adnexa were easily controlled using salvage RT.

The current study found that SP occurred at a greater frequency in patients with secondary lymphoma ($p = 0.002$), bilateral disease ($p = 0.004$), and advanced stage ($p < 0.001$) at diagnosis, but was not associated with tumor location ($p = 0.547$). However, no conjunctival lymphoma patients died from the disease or developed systemic relapse. Unlike in previous reports, lacrimal gland MALT lymphoma patients showed a favorable outcome, as seen in Table 7 (www.op-rs.com, Article Plus), while one case of eyelid lymphoma had a poor prognosis, as reported previously.[2,7,12] Eyelid lymphomas are reported to have a more aggressive course than orbital or conjunctival lesions,[2,7] while lacrimal gland lesions are reported to be associated with more frequent and earlier extraorbital lymphomas.[12] Conjunctival lymphomas are reported as having a good prognosis.[1,2,7,10,12] Martinet et al. found the conjunctival location was a favorable factor for disease free survival and freedom from treatment failure after RT for lymphoma.[13] On the contrary, Cho et al. reported that conjunctival MALT lymphomas had a similar or slightly worse prognosis than those at other sites.[5]

Of the 3 patients with bilateral conjunctival MALT lymphomas in whom only symptomatic unilateral eyes were treated, tumor regrowth occurred in 1 untreated eye at 8 years after initial diagnosis, and disappeared immediately following RT. For the other 2 lesions, tumor mass in untreated eyes decreased up to 78 and 80 months after diagnosis. Conjunctival MALT lymphomas were reported to spontaneously regress without treatment over 1 to 11 years from diagnosis.[28] Others found that low grade B cell lymphomas are prone to regress spontaneously and do not necessarily recur even after incomplete resection.[29]

Several reports emphasize the need for lifetime follow-up given the tendency for recurrence in other organs with MALT tissues.[9] Studies of 101 primary conjunctival lymphoma patients found systemic spread in 7% of patients after 1 year,[25] and in 28% after 10 years.[30] Jenkins et al.[12] reported that long term follow-up was necessary, because the risk of mortality continues to exist after many years. In the present study, only one primary lymphoma patient exhibited SP, this being at a single site (right shoulder), and it was easily controlled by surgical resection. This patient was recurrence free and showed no internal organ involvement during 108 months of follow-up. In contrast to the low frequency in primary patients, 50% of secondary lymphoma patients showed SP. These results suggest that extensive lifetime follow-up studies are not essential in the management of low grade ocular adnexal lymphomas, if the patient does not have disseminated disease outside the orbit at presentation.

The present study identified one case of a diffuse large B cell lymphoma in the lacrimal sac, and one case of bilateral lower fornix conjunctivas. No local or extraorbital relapse was detected during the median follow-up period of 25 months after chemotherapy. The favorable outcome of the diffuse large B cell lymphoma, classified as highly malignant according to WHO, may be related to the ocular adnexal location and the IAE stage.

Lymphomas of the NK/T cell subtype are extremely rare in the ocular adnexa. The present study identified one case of bilateral NK/T cell lymphoma, which was

CD-56 positive and of the nasal type. This nasal type of extranodal NK/T cell lymphoma is reported to have a higher incidence in Asian populations compared with Western populations.[31] The NK/T cell lymphoma in the current study was aggressive, and the patient died of systemic invasion within 3 months of combined chemotherapy and RT.

Local RT is the treatment of choice for patients with disease originating in the ocular adnexa. In the present study, 81.8% of lesions (63 eyes) were treated with RT, leading to an 88.9% (56 eyes) CR rate, and a 100% overall remission rate including partial response in the local lesions. Most patients received 25 Gy to 30.6 Gy RT at 1.8 Gy to 2.0 Gy per fraction. One patient with a bilateral conjunctival mass received 5.4 Gy in 3 fractions, and the tumor was undetectable within a few weeks. A dose of less than 30 Gy is recommended to minimize RT complications.[32]

In conclusion, over 90% of ocular adnexal lymphomas in Koreans were found to be MALT lymphomas. This subtype shows indolent clinical behavior and a tendency to present as localized at diagnosis, and it was rarely found to spread extraorbitally. Patients with symptomatic relapse were successfully treated using salvage RT at the time of relapse. It appears extensive follow-up study is not essential in the management of low grade primary MALT ocular adnexal lymphomas. In addition, the present study confirmed the association of stage, bilaterality at presentation, and status (primary or secondary) with CSS and SP. There was no single variable that correlated with RFS according to univariate analysis. The single most important and statistically significant prognostic factor was the extent of disease (stage) at diagnosis. Studies involving longer follow-up periods and larger numbers of patients will provide further knowledge regarding late relapse rates and prognostic factors associated with relapse in ocular adnexal MALT lymphoma patients.

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